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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 6

Application Number	10/550,608
Filing Date	September 26, 2005
First Named Inventor	Martinez, et al.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	ABG 3008

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
- [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [x] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

4 Exhibits, Return Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Kramer & Amado, P.C.		
Signature			
Printed name	Andreas Baltatzis		
Date	4/19/06	Reg. No.	56,794

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/17 (01-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2006

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)	200.00

Complete if Known	
Application Number	10/550,608
Filing Date	September 26, 2005
First Named Inventor	Martinez, et al.
Examiner Name	Unassigned
Art Unit	Unassigned
Attorney Docket No.	Unassigned

METHOD OF PAYMENT (check all that apply)

☐ Check ☑ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 500578 Deposit Account Name: Terry W. Kramer

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

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FEE CALCULATION (All the fees below are due upon filing or may be subject to a surcharge.)

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
_____ - 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____ - 100 =	_____	/ 50 = _____ (round up to a whole number)	x _____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Petitions requiring the petition fee set forth in 37 CFR 1.17(q)	$200

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 56,794	Telephone 703-519-9801
Name (Print/Type)	Andreas Baltatzis		Date 4/19/06

PATENT

IN THE UNITED STATE PATENT AND TRADEMARK OFFICE

In re application of:	:	Martínez et al.
For:	:	IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA
Serial No.	:	10/550,608
Filed	:	September 26, 2005
Art Unit	:	Unassigned
Examiner	:	Unassigned
Attorney Docket No.	:	ABG 3008
Confirmation No.	:	Unassigned

PETITION TO FILE ON BEHALF OF INVENTOR WHO REFUSES TO JOIN IN APPLICATION UNDER 37 C.F.R. § 1.47

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

One of the joint inventors of the above referenced application has refused to join in the application for patent. Therefore, the Applicants hereby petition to make the application on their behalf and the nonsigning inventor.

A *bona fide* attempt to comply with the requirements of 37 C.F.R. § 1.47 has been made as discussed in detail below.

The pertinent facts of the case have been presented in a letter from the Assignee's Foreign Legal Representative attached as Exhibit A. The Assignee and the Assignee's Legal Representative have performed the following steps on the Applicants' behalf in order to contact the nonsigning inventor, Miguel Molina Vila:

1. On September 29, 2005, the Assignee, PROGENIKA BIOPHARMA, S.A. mailed a copy of the Assignment and Declaration and Power of Attorney to the last known address of the nonsigning inventor, along with a copy of the abstract of the PCT application. The mailing is attached as Exhibit B. The nonsigning inventor did not reply to the first letter.
2. On November 3, 2005, the Assignee, PROGENIKA BIOPHARMA, S.A. mailed a copy of the Assignment and Declaration and Power of Attorney to the last known address of the nonsigning inventor, along with copies of the Assignment and Declaration and Power of Attorney signed by all of the other inventors. The mailing is attached as Exhibit C. The nonsigning inventor did not reply to the second letter.
3. Following the lack of response by the nonsigning inventor, the Applicants attempted to locate the inventor through the Spanish equivalent of the personal phone directory or "Yellow Pages" and discovered that the nonsigning inventor was not listed.
4. The Assignee's Legal Representative, ABG PATENTES obtained the email address of the inventor. On February 7, 2006, the ABG PATENTES emailed the nonsigning inventor electronic copies of the Assignment and Declaration and Power of Attorney. The nonsigning inventor replied through email asking for the best way to sign and return the documents.
5. On February 8, 2006, the nonsigning inventor wrote an email asking to change the address on the Declaration and Power of Attorney to his new home address without providing the address. The nonsigning inventor also asked if he would lose ownership rights in the patent application by signing the assignment.
6. On February 9, 2006, ABG PATENTES responded to the inventor stating that they would change the address in the Declaration and Power of Attorney if provided. Also, ABG PATENTES stated that according to the nonsigning inventor's contract signed with Assignee, the nonsigning inventor was required to assign all ownership rights in the patent application to the Assignee. A copy of the contract was included with the email.
7. The nonsigning inventor did not respond to the email dated February 9, 2006.
8. ABG PATENTES emailed a reminder to the nonsigning inventor on February 15, 2006 and did not receive a response.
9. ABG PATENTES emailed a reminder to the nonsigning inventor on February 20, 2006 and did not receive a response.
10. ABG PATENTES emailed a reminder to the nonsigning inventor on March 9, 2006 that included copies of the application documents as filed in the U.S.P.T.O., and the assignment documents. The nonsigning inventor did not respond to the email of March 9, 2005.

We have attached the email correspondence between the nonsigning inventor and ABG PATENTES summarized above as Exhibit D.

The last known address of the nonsigning inventor is:

Miguel Molina Vila
C/ Pintura 1, 5°, 2ª
08035- Barcelona

A *bona fide* attempt to comply with the requirements of 37 C.F.R. § 1.47 has been made as discussed in detail below. The nonsigning inventor has refused to join in the signing of the application.

In view of the above, Applicants request that the Petition be granted.

Respectfully submitted,

4/19/06
Date

Andreas Baltatzis
Reg. No. 56,794

KRAMER & AMADO, P.C.

patentes
ARIAS , BERNARDO & GONZÁLEZ
Asesoría y Agencia de la Propiedad Industrial
Intellectual Property

RECEIVED
MAR 09 2006
Kramer & Amado, P.C.

KRAMER & AMADO, P.C.
1725 Duke Street, Suite 240
Alexandria, Virginia 22314
United States

Atn.:Arlir Amado

Via Facsimile
Confirmation by mail

Our ref.: P1121USPC
Your ref.: ABG 3008

Madrid, March 3, 2006

Re: Patent Application in United States No. 10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA", in the name of PROGENIKA BIOPHARMA, S.A.

Dear Sirs,

Further to your mail dated January 31, 2006, please be informed that in order to get the signature of the inventor (Miguel Angel Molina), the following steps have been performed:

- First of all, the Applicant sent the documentation two or three times to the last known address of the inventor, but there was no answer. Then, the applicant tried to locate him per "yellow pages" of the Spanish Telephone Company, but there was no input under his name.

- Afterwards, ABG Patentes got the e-mail address of the inventor by chance (through an indirect personal contact).

- On February 7, 2005, ABG Patentes sent Miguel Angel Molina via e-mail the documents of "Assignment" and "Declaration and Power of Attorney". He answered to this e-mail asking how is the better way to return us these documents once signed. We answered this question thinking that he was ready to cooperate.

- On February 8, 2006, he wrote again asking whether it was possible to change the address of the document of "Declaration and Power of Attorney" to his home address and, also, that if the signature of the document of "Assignment" meant to loose his rights over this patent application.

- On February 9, 2006, we answered to his questions saying that we would change his address in the document of "Declaration and Power of Attorney", and that if he signed the document he would loose indeed, any kind of rights over the patent. We continued by saying that according to the Spanish Patent Law, and according to the contract he signed with the Applicant, the inventions made during his stay in the company are considered to belong to the company he works or worked for.

- After our last e-mail (February 9, 2006), we sent him two reminders about this matter, one on February 15, 2006 and the other one on February 20, 2006, but the inventor has not answered yet. Moreover, we believe the inventor will never answer back. Unfortunately, we could only get his e-mail address, not his home or work address.

This is the present situation for this case. Therefore, we would appreciate if you could inform us what would be the following step with respect to the filing of the Assignment" and "Declaration and Power of Attorney" before the USPTO

Best regards,

Juan Arias Sanz
European Patent Attorney
ABG Patentes, S.L.

CD000246979979

Correos y Telégrafos

ESPACIO PARA CÓDIGO DE BARRAS
BARRA-KODERAKO GUNEA

CIF:A83052407 OFICINA:4801611 ARTEAGA-DERIO

REMITENTE/BIDALTZAILEA

D. PROTEOMICA NIF B-62793526

DESTINATARIO/HARTZAILEA

D. NIGUEL ANGEL MOLINA VILA

C/ Población Herria: C/ PINTURA nº 1 piso 5º 2ª Zkia solairua

C.P. 08035 Prov. Prob.: BARCELONA País Herrialdea: ESPAÑA

Carta Certificada
Fecha:29/09/2005
Peso: 144 gr.
Hora:09:09
Importe: 2,83 €

Sello de fechas o validación mecánica
Data-zigilua, edo makinaz baliozkotua

MODALIDAD / GENERO: ☒ Carta ☐ Paquete Postal ☐ Impreso ☐ Paquete Azul — PESO: grs.

☐ Reembolso/Ordainketaren truke — Euros

☐ Asegurada/Aseguruduna — Euros

INFORMACIÓN 902 197 197 INTERNET www.correos.es

SOCIEDAD ESTATAL CORREOS Y TELÉGRAFOS, S.A. VÍA DUBLIN, 7 C.P. 28042 MADRID REG. MERCANTIL DE MADRID Tomo 16.665 Libro 0 Folio 20 Sec. 8 Hoja M284323 Inscrip. 1 C.I.F. A83052407

PROGENIKA S.A.
Edificio 801 . Parque Tecnológico de Zamudio
48160 Derio . Spain
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
www.progenika.com

PROGENIKA

D. Miguel Ángel Molina Vila.

DNI: 33895291F

C/ Pintura 1, 5º 2ª. 08035 Barcelona

Estimado Dr. Molina:

Usted figura como inventor en la solicitud de patente de Progenika biopharma, SA. WO2004085676. Para confirmar su aceptación en el proceso de solicitud en la United States Patent Office, es necesario que firme los documentos que se adjuntan (El documento Assignment es necesario que lo firme adicionalmente un testigo) y los envíe a la siguiente dirección:

Laureano Simón.
Progenika biopharma, SA
Parque Tecnológico de Vizcaya. 801-B.
48160, Derio, Vizcaya.

Agradeciéndole su colaboración, le saluda atentamente,

Laureano Simón.
Progenika biopharma, SA

Assignment of Patent Application

Whereas, we, **Antonio Martínez Martínez, Laureano Simón Buela, Simón Santa Cruz, María Pilar Sáenz Jiménez, Miguel Molina Vila, Corina Junquera Sánchez-Vallejo, José Javier Gómez Román and Jorge Cuevas González,** hereafter referred to as applicants, have invented certain new and useful improvements relating to an **IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA**

[ ] for which an application for a United States patent was filed on _____, Application Number _____.

[ ] for which an application for a United States Patent was executed on _____, and

Whereas, **PROGENIKA BIOPHARMA, S.A.,** herein referred to as assignee, whose post office address is **Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª plantaE-48160 - DERIO – Vizcaya, Spain,** is desirous of acquiring the entire right, title and interest in the same:

Now, therefore, in consideration of the sum of ten dollars ($10.00), the receipt whereof is acknowledged, and other good and valuable consideration, we, the applicants, by these presents do sell, assign and transfer unto said assignee the full and exclusive right to the said invention in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof, and the entire right, title and interest in and to any and all Patents which may be granted therefor in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof. we hereby authorize and request the Commissioner of Patents and Trademarks to issue said United States Patent to said assignee, of the entire right, title, and interest in and to the same, for its sole use and behoof; and for the use and behoof of its legal representatives, to the full end of the term for which said Patent may be granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

The undersigned hereby grant the firm of Kramer and Amado, P.C. the power to insert on this document any identification which may be necessary or desired to reference the property being transferred under the rules of the United States Patent and Trademark Office for recordation purposes.

EXECUTED THIS __ day of _____, 20___, at _____

_____ _____

Antonio Martínez Martínez Date

_____

Witness

Assignment of Patent Application

Laureano Simón Buela _____ Date _____

Witness _____

Simón Santa Cruz _____ Date _____

Witness _____

María Pilar Sáenz Jiménez _____ Date _____

Witness _____

Corina Junquera Sánchez-Vallejo _____ Date _____

Witness _____

José Javier Gómez Román _____ Date _____

Witness _____

Jorge Cuevas González _____ Date _____

Witness _____

Assignment of Patent Application

_____ _____

Miguel Molina Vila Date

_____

Witness

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

As a below named inventor, I hereby declare that:
My residence/post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA
the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: X NO:
			YES: NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Power of Attorney:
As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to:	Direct telephone calls to:
Arlir M. Amado Kramer & Amado, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Phone: (703) 519-9801 Fax: (703) 519-9802	Arlir M. Amado (703) 519-9801

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Antonio Martínez Martínez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Laureano Simón Buela Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Simon Santa Cruz Citizenship: Great Britain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: María Pilar Sáenz Jiménez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Corina Junquera Sánchez-Vallejo Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: José Javier Gómez Román Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/nE-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Jorge Cuevas González Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/nE-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: Miguel Molina Vila Citizenship: Spain

Residence: C/ Pintura 1, 5° 2ª. E-08035 Barcelona, Spain

Post Office Address: Same

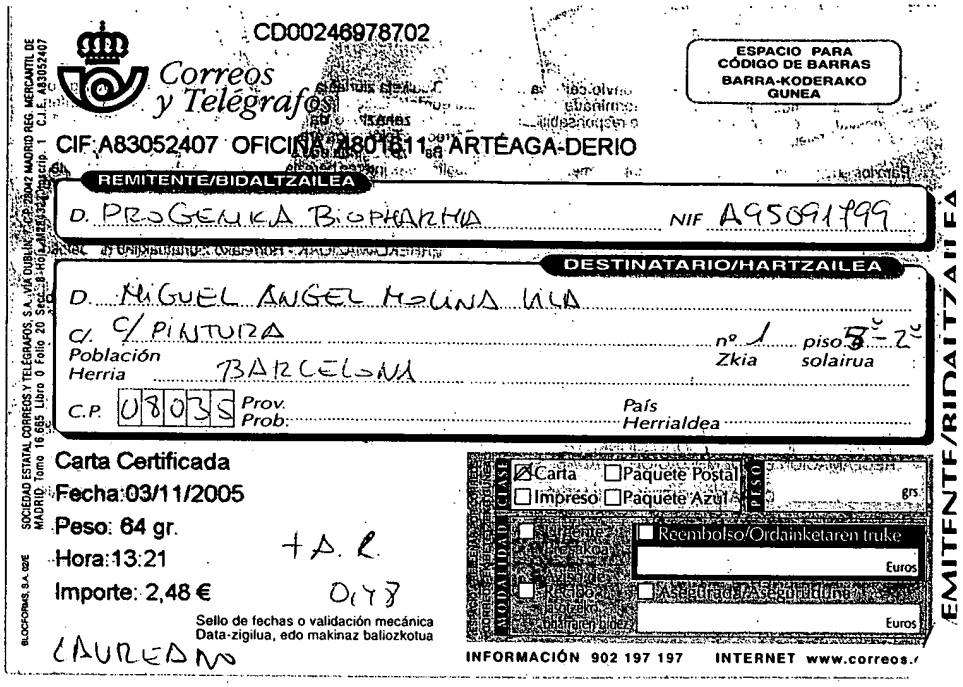
Inventor's Signature Date

IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

Patent number: WO2004085676
Publication date: 2004-10-07
Inventor: MARTINEZ MARTINEZ ANTONIO (ES); SIMON BUELA LAUREANO (ES); SANTA CRUZ SIMON (ES); SAENZ JIMENEZ MARIA PILAR (ES); MOLINA VILA MIGUEL (ES); JUNQUERA SANCHEZ-VALLEJO CORIN (ES); GOMEZ ROMAN JOSE JAVIER (ES); CUEVAS GONZALEZ JORGE (ES)
Applicant: MEDPLANT GENETICS S L (ES);; MARTINEZ MARTINEZ ANTONIO (ES);; SIMON BUELA LAUREANO (ES);; SANTA CRUZ SIMON (ES);; SAENZ JIMENEZ MARIA PILAR (ES);; MOLINA VILA MIGUEL (ES);; JUNQUERA SANCHEZ-VALLEJO CORIN (ES);; GOMEZ ROMAN JOSE JAVIER (ES);; CUEVAS GONZALEZ JORGE (ES)
Classification:
- international: C12Q1/68; G01N33/574
- european: G01N33/574C
Application number: WO2004EP03219 20040325
Priority number(s): ES20030000708 20030326

Cited documents:
WO0068424
WO0210285
XP00218167
XP0010309

Abstract of **WO2004085676**
The present invention refers to an in vitro method to detect a bladder transitional cell carcinoma, in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of therapy administered to an individual with this cancer; to screen for, identify, develop and evaluate the efficacy of therapeutic compounds against this cancer in order to develop new medicinal products, and also agents that inhibit the expression and/or activity of the FGFR3 protein and/or the effects of this expression.



CD00246978702

Correos y Telégrafos

ESPACIO PARA CÓDIGO DE BARRAS
BARRA-KODERAKO GUNEA

CIF A83052407 OFICINA 280161 ARTEAGA-DERIO

REMITENTE/BIDALTZAILEA

D. PROGENIKA BIOPHARMA NIF A95091799

DESTINATARIO/HARTZAILEA

D. MIGUEL ANGEL MOLINA VILA

C/ C/ PINTURA nº 1 piso 3º-2ª
Población Herria BARCELONA Zkia solairua

C.P. 08035 Prov. Prob: País Herrialdea

Carta Certificada
Fecha:03/11/2005
Peso: 64 gr.
Hora:13:21
Importe: 2,48 €

+A.R. 0,78

Sello de fechas o validación mecánica
Data-zigilua, edo makinaz baliozkotua

LAUREANO

MODALIDAD CLASE: ☑ Carta ☐ Paquete Postal ☐ Impreso ☐ Paquete Azul
PESO: grs
☐ Reembolso/Ordainketaren truke Euros
☐ A.R. ☐ A.S. Euros

INFORMACIÓN 902 197 197 INTERNET www.correos.

EMITENTE/BIDALTZAILEA

SOCIEDAD ESTATAL CORREOS Y TELÉGRAFOS, S.A. VÍA DUBLIN 7 28042 MADRID REG. MERCANTIL DE MADRID Tomo 16.665 Libro 0 Folio 20 Sección 8 Hoja M-267543 Insc.1ª C.I.F. A83052407

BLOCFORMS, S.A. 026

PROGENIKA S.A.
Edificio 801 . Parque Tecnológico de Zamudio
48160 Derio . Spain
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www.progenika.com

PROGENIKA

D. Miguel Ángel Molina Vila.

DNI: 33895291F

C/ Pintura 1, 5º 2ª. 08035 Barcelona

Estimado Dr. Molina:

Usted figura como inventor en la solicitud de patente de Progenika biopharma, SA. WO2004085676. Para confirmar su aceptación en el proceso de solicitud en la United States Patent Office, es necesario que firme los documentos que se adjuntan (El documento Assignment es necesario que lo firme adicionalmente un testigo) y los envíe a la siguiente dirección:

Laureano Simón.
Progenika biopharma, SA
Parque Tecnológico de Vizcaya. 801-B.
48160, Derio, Vizcaya.

Agradeciéndole su colaboración, le saluda atentamente,

Laureano Simón.
Progenika biopharma, SA

Assignment of Patent Application

Whereas, we, **Antonio Martínez Martínez, Laureano Simón Buela, Simon Santa Cruz, María Pilar Sáenz Jiménez, Miguel Molina Vila, Corina Junquera Sánchez-Vallejo, José Javier Gómez Román and Jorge Cuevas González**, hereafter referred to as applicants, have invented certain new and useful improvements relating to an **IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA**

[ ] for which an application for a United States patent was filed on _____, Application Number _____.

[ ] for which an application for a United States Patent was executed on _____, and

Whereas, **PROGENIKA BIOPHARMA, S.A.**, herein referred to as assignee, whose post office address is **Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª plantaE-48160 - DERIO – Vizcaya, Spain**, is desirous of acquiring the entire right, title and interest in the same:

Now, therefore, in consideration of the sum of ten dollars ($10.00), the receipt whereof is acknowledged, and other good and valuable consideration, we, the applicants, by these presents do sell, assign and transfer unto said assignee the full and exclusive right to the said invention in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof, and the entire right, title and interest in and to any and all Patents which may be granted therefor in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof. we hereby authorize and request the Commissioner of Patents and Trademarks to issue said United States Patent to said assignee, of the entire right, title, and interest in and to the same, for its sole use and behoof; and for the use and behoof of its legal representatives, to the full end of the term for which said Patent may be granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

The undersigned hereby grant the firm of Kramer and Amado, P.C. the power to insert on this document any identification which may be necessary or desired to reference the property being transferred under the rules of the United States Patent and Trademark Office for recordation purposes.

EXECUTED THIS __ day of _____, 20___, at _____

_____ _____

Antonio Martínez Martínez Date

_____

Witness

Assignment of Patent Application

Laureano Simón Buela _____ Date _____

Witness _____

Simón Santa Cruz _____ Date _____

Witness _____

María Pilar Sáenz Jiménez _____ Date _____

Witness _____

Corina Junquera Sánchez-Vallejo _____ Date _____

Witness _____

José Javier Gómez Román _____ Date _____

Witness _____

Jorge Cuevas González _____ Date _____

Witness _____

Assignment of Patent Application

Miguel Molina Vila _____ Date _____

Witness _____

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

As a below named inventor, I hereby declare that:
My residence/post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA
the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: X NO:
			YES: NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE

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Power of Attorney:
As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to:	Direct telephone calls to:
Arlir M. Amado Kramer & Amado, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Phone: (703) 519-9801 Fax: (703) 519-9802	Arlir M. Amado (703) 519-9801

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Antonio Martínez Martínez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

_____ _____
Inventor's Signature Date

Full Name of Inventor: Laureano Simón Buela Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

_____ _____
Inventor's Signature Date

Full Name of Inventor: Simon Santa Cruz Citizenship: Great Britain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

_____ _____
Inventor's Signature Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: María Pilar Sáenz Jiménez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Corina Junquera Sánchez-Vallejo Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: José Javier Gómez Román Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/nE-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Jorge Cuevas González Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/nE-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: Miguel Molina Vila Citizenship: Spain

Residence: C/ Pintura 1, 5° 2ª. E-08035 Barcelona, Spain

Post Office Address: Same

Inventor's Signature Date

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IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA
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PCT	PCT/EP04/003219	03/25/2004	YES: NO: X
Spain	P200300708	03/26/2003	YES: X NO:

Provisional Application
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I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

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As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date 24.Oct.2005

Full Name of Inventor: Laureano Simón Buela Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date 24.Oct.2005

Full Name of Inventor: Simon Santa Cruz Citizenship: Great Britain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date 24.Oct.2005

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: María Pilar Sáenz Jiménez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature 24/10/2005 Date

Full Name of Inventor: Corina Junquera Sánchez-Vallejo Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Corina Junquera 24.oct.2005
Inventor's Signature Date

Full Name of Inventor: José Javier Gómez Román Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/nE-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature 24.oct.2005 Date

Full Name of Inventor: Jorge Cuevas González Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/nE-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature 24.oct.2005 Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 CUSTOMER NUMBER: 30868

Full Name of Inventor: Miguel Molina Vila Citizenship: Spain

Residence: C/ Pintura 1, 5° 2ª. E-08035 Barcelona, Spain

Post Office Address: Same

Inventor's Signature Date

Assignment of Patent Application

Whereas, we, **Antonio Martínez Martínez, Laureano Simón Buela, Simón Santa Cruz, María Pilar Sáenz Jiménez, Miguel Molina Vila, Corina Junquera Sánchez-Vallejo, José Javier Gómez Román and Jorge Cuevas González**, hereafter referred to as applicants, have invented certain new and useful improvements relating to an **IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA**

[ ] for which an application for a United States patent was filed on _____, Application Number _____.

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Whereas, **PROGENIKA BIOPHARMA, S.A.**, herein referred to as assignee, whose post office address is **Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - B 2ª plantaE-48160 - DERIO – Vizcaya, Spain**, is desirous of acquiring the entire right, title and interest in the same:

Now, therefore, in consideration of the sum of ten dollars ($10.00), the receipt whereof is acknowledged, and other good and valuable consideration, we, the applicants, by these presents do sell, assign and transfer unto said assignee the full and exclusive right to the said invention in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof, and the entire right, title and interest in and to any and all Patents which may be granted therefor in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof. we hereby authorize and request the Commissioner of Patents and Trademarks to issue said United States Patent to said assignee, of the entire right, title, and interest in and to the same, for its sole use and behoof; and for the use and behoof of its legal representatives, to the full end of the term for which said Patent may be granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

The undersigned hereby grant the firm of Kramer and Amado, P.C. the power to insert on this document any identification which may be necessary or desired to reference the property being transferred under the rules of the United States Patent and Trademark Office for recordation purposes.

EXECUTED THIS __ day of _____, 20___, at _____

_____ 24.Oct.2005

Antonio Martínez Martínez — Date

_____

Witness

Assignment of Patent Application

Laureano Simón Buela — Date: 24.Oct.2005

MARTA ARTIEDA OSSÑALDE

Witness

Simón Santa Cruz — Date: 24.Oct.2005

MARCELINO FERRER ALCÓN

Witness

María Pilar Sáenz Jiménez — Date: 24/10/2005

Gorka Ochoa Garay

Witness

Corina Junquera Sánchez-Vallejo — Date: 24.Oct.2005

Berna del Prado

Witness

José Javier Gómez Román — Date: 24.Oct.2005

Witness

Jorge Cuevas González — Date: 24.Oct.2005

Witness

Assignment of Patent Application

_____ _____

Miguel Molina Vila Date

_____

Witness

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: jueves, 09 de marzo de 2006 16:05
Para: 'miguelamol@hotmail.com'
CC: Juan Arias (jarias@abgpatentes.com); 'Laureano'
Asunto: Solicitud de patente en Estados Unidos No. 10/550,608-N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Molina:

Como continuación a nuestro e-mail de fecha 20 de febrero de 2006, le remitimos de nuevo los documentos de "Assignment" y "Declaration and Power of Attorney" para que sean debidamente firmados. En el documento de "Declaration and Power of Attorney" hemos dejado en blanco el campo de su dirección para que si lo desea lo rellene con su actual dirección.

Por otro lado, le adjuntamos copia de la solicitud tal y como fue presentada ante la Oficina Norteamericana de Patentes (USPTO). También le remitimos copia de la notificación emitida por la USPTO en la que nos confirmaban la fecha de presentación (**26 de septiembre de 2006**) así como el número que le había correspondido, **10/550,608.**

En espera de sus noticias le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
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Assignment of Patent Application

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María Pilar Sáenz Jiménez _____ Date _____

Witness _____

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José Javier Gómez Román _____ Date _____

Witness _____

Jorge Cuevas González _____ Date _____

Witness _____

Assignment of Patent Application

Miguel Molina Vila

Date

Witness

PATENT APPLICATION

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Spain	P200300708	03/26/2003	YES: X NO:

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Full Name of Inventor: Antonio Martínez Martínez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Laureano Simón Buela Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Simón Santa Cruz Citizenship: Spain

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PATENT APPLICATION

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ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: María Pilar Sáenz Jiménez Citizenship: Spain

Residence: Edificio 801A, Parque Tecnológico de Zamudio, E-48160 Derio, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Corina Junquera Sánchez-Vallejo Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

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Inventor's Signature Date

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Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/n E-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Jorge Cuevas González Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/n E-39008 Santander, Spain

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Full Name of Inventor: Miguel Molina Vila Citizenship: Spain

Residence: _____

Post Office Address: Same

_____ _____

Inventor's Signature Date

Atty. Docket: ARG 3008 Today's Date: September 26, 2005
Applicants: Antonio Martínez Martínez, et al.
Serial No.: New
Filing Date: September 26, 2005
Title: IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

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- Transmittal Letter to the U.S. Designated/Elected Office Concerning Submission Under 35 U.S.C. 371 (2 pages)
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- Application Data Sheet (6 pages)
- Patent Application including Claims 1-29, Figs. 1-5 and sequence listing (4 pages)
- Copy of PCT Application No. PCT/EP04/003219

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1725 Duke Street, Suite 240
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Atty. Docket: ABG 3008 Today's Date: September 26, 2005
Applicants: Antonio Martínez Martínez, et al.
Serial No.: New
Filing Date: September 26, 2005
Title: IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

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- Patent Application including Claims 1-29, Figs. 1-5 and sequence listing (41 pages)
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PTO-1390 (Rev. 02-2005)
Approved for use through 3/31/2007. OMB 0651-0021
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TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
ABG 3008	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP04/003219	March 25, 2005	March 26, 2003

TITLE OF INVENTION
IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

APPLICANT(S) FOR DO/EO/US
Antonio Martinez Martinez, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☑ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☑ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A preliminary amendment.
14. ☑ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821- 1.825.
18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☐ Other items or information:

PTO-1390 (Rev. 02-2005)
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U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/EP04/003219	ABG 3008

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. ☑ Basic national fee..... $300	$ 300.00	
22. ☑ Examination fee If International preliminary examination report prepared by USPTO and all claims satisfy provisions of PCT Article 33(1)-(4)..... $100 All other situations..... $200	$ 200.00	
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☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $250 for each additional 50 sheets of paper or fraction thereof.		

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CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE	$	
Total claims	40	- 20 =	20	x $ 50	$ 1000.00	
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MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+ $360	$ 360.00	
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☑ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.						
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SEND ALL CORRESPONDENCE TO:
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SIGNATURE

Arlir M. Amado
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APPLICATION DATA SHEET

Application Information

Application Number::	New
Filing Date::	09/26/05
Application Type::	Regular
Subject Matter::	Utility
Suggested Classification::	None
CD-ROM or CD-R?::	None
Sequence Submission::	Paper
Computer Readable Form (CRF)?::	Yes
Number of Copies of CRF::	1
Title::	IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA
Attorney Docket Number::	ABG 3008
Request for Early Publication?::	No
Suggested Drawing Figure::	None
Total Drawing Sheets::	5
Small Entity?::	Yes
Petition Included?::	No
Licensed US Govt. Agency::	None

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Representative Information

Representative Customer Number::	30868

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::
PCT	PCT/EP04/003219	03/25/04	Yes
Spain	P200300708	03/26/03	Yes

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IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA

FIELD OF THE INVENTION

The present invention refers to an *in vitro* method to detect the presence of a transitional cell carcinoma of the bladder in an individual, to determine the stage or severity of this cancer in the individual, or to monitor the effect of therapy administered to an individual with the said cancer; to screen for, identify, develop and evaluate the efficacy of therapeutic compounds for this cancer in an attempt to develop new medicinal products and to agents that inhibit expression and/or the activity of the FGFR3 protein.

BACKGROUND OF THE INVENTION

Despite all the advances that have been achieved during the last 20 years, cancer is still one of the leading causes of mortality worldwide. Transitional cell bladder cancer is the most common cancer of the urinary tract; it is also the fourth most common cancer in men and the eight most common in women. Based on data from the International Agency for the Investigation of Cancer, GLOBOCAN, for the year 2000, more than 136.000 new cases per year are diagnosed in Europe, 13.000 in Japan and 56.000 in North America. More than 3-4 times this number of patients are treated and monitored at hospitals every year; and more than 49.000, 4.500 and 12.000 deaths are due to bladder cancer every year in Europe, Japan and North America, respectively (according to the International Agency for Research on Cancer GLOBOCAN 2000).

Transitional cell carcinoma (TCC) is the most common type of *bladder cancer*, accounting for more than 90% of all cases. The remaining cases are squamous cell carcinomas (7%), adenocarcinomas (2%), and undifferentiated carcinomas (1%).

Tumour grade and stage are the best prognostic indicators of transitional cell carcinoma of the bladder. Bladder tumours are graded cytomorphologically from G1 to G3 in decreasing state of differentiation and increasing aggressiveness of the disease according to the World Health Organization (WHO). With respect to stage or invasivity, TCCs of the bladder are classified as superficial papillary (Ta and T1), muscle invasive (T2 to T4), or the uncommon carcinoma in situ or tumour in situ (TIS).

Low-grade (G1) tumours are usually confined to the mucosa or infiltrate superficial layers (stage Ta and T1). Most high-grade tumours are detected at least at T1 stage (invading lamina propria). Approximately 75% of the diagnosed bladder cancer cases are superficial. The remaining 25 % are muscle invasive at the moment of diagnosis.

The clinical importance of distinguishing superficial and invasive tumours stems from the need to perform radical cystectomy, with lymphadenectomy and bladder reconstruction in case of extended cancers (beyond the muscular layer). Tumours diagnosed in stages Ta and T1 allow the organ to be preserved and can be treated by transurethral resection and in some cases chemotherapy or intravesicular immunotherapy.

Patients with superficial TCC have a good prognosis but have a 70 % risk of recurrence; these patients have to be monitored for tumour recurrence after treatment, following different protocols depending on the hospital, although the most frequent method is evaluation by the urologist every 3 months during the first 2 years, every 6 months for the following 2 years and every year thereafter. In spite of the high risk of recurrence, Ta tumours tend to be low grade and only 10-15% will progress to muscle invasion in 2 years; the percentage of T1 tumours that progresses to T2 stage is higher (30-50%).

Patients with invasive TCC have a poor prognosis; 50% of these patients at stage T2 or higher develop distant metastases within two years of diagnosis, and 69% of them die within 5 years. New diagnosis systems for early detection are needed given that 80-90 % of patients with T2 or higher are first diagnosed at this highly aggressive stage and not in previous stages (de Vere White, R.W. and Stapp, E., Oncology, 1998, 12:1717-1723).

Currently, the best diagnostic system for bladder cancer in individuals presenting symptoms such as hematuria or dysuria, in the absence of infection, is cytoscopy. Based on statistical data of incidence and recurrence, it has been estimated that more than 500.000 cystoscopies are performed annually in the USA (van Rhijn, B.W.G., et al., Cancer Res., 2001, 61:1265-1268). Flexible cytoscopes are used to make the technique less aggressive, but it remains invasive and highly unpleasant, and it also requires some form of anaesthesia.

The prevailing non-invasive technique for diagnosis of transitional cell bladder cancer is to identify neoplastic cells by morphological examination of the cells in urine (Loh, C.S., et al., Br. J. Urol., 1996, 77:655-658). Cytology is currently used to follow up patients diagnosed with and treated for bladder cancer. On the other hand urine cytology can detect tumours *in situ* that are not detectable by cytoscopy as well as tumours located in the upper end of the bladder or the upper urinary tract, i.e. ureter, pelvis and renal, that are not easily accessible by endoscopy (Lotan, Y. and Roehrborn, J. Urol., 2002, 167:75-79).

Nevertheless several studies have shown that cytology has a very low sensitivity for bladder cancer diagnosis, missing up to 50% of tumours (Boman, H., et al., J. Urol., 2002, 167:80-83); in reality, there is no non-invasive method available to diagnose bladder cancer with high sensitivity and specificity (Boman, H., et al., J. Urol., 2002, 167:80-83). Such non-invasive methods would allow routine screening procedures for early detection of any

transitional carcinoma including of the upper urinary tract, both *de novo* or in evaluating recurrence after treatment, including the detection of incipient invasive tumours or those at a high risk of developing aggressive disease.

Alteration of gene expression levels is tightly associated to uncontrolled cell growth and de-differentiation, common features of all cancers. The expression levels of the so-called "tumour suppressor genes", which act to block malignant cell growth, are repressed in tumour cells; and expression levels of the so-called "oncogenes", which act to induce malignant growth, are elevated in tumour cells.

Many of these genes have been associated to bladder cancer development, including Rb, p53, p16, p14ARF, cyclin D1 (Fujimoto, K., et al., Cancer Res., 1998, 52:1393-1398; Grossman, B.H., et al., Clin. Cancer Res., 1998, 8:829-834; Balazs, M., et al., Genes Chromosomes Cancer, 1997, 19:84-89). The alteration in the expression of these genes could be used as a diagnostic marker of transitional cell carcinoma of the bladder; among these proposed markers have been proposed nuclear matrix protein NMP22 (Soloway, M.S., et al., J. Urol., 1996, 156:363-367; Casella, R., et al., J. Urol, 2000, 164:1926-1928), Hyaluronic Acid and Hyaluronidase (Pham, H.T., et al., Cancer Res., 1997, 57:778-783; Hautmann, S.H., et al., J. Urol., 2001, 165:2068-2074), Basement Membrane Complexes (BTA) (Pode, D., et al., J. Urol., 1999, 161:443-446; Thomas, L., et al., Clin. Chem, 1999, 45:472-477, Carcinoembryonic antigen (CEA) (Halim, A.B., et al., Int. J. Biol. Markers, 1992; 7:234-239), Uroplakin II (Wu, X.R., et al., Cancer Res., 1998; 58:1291-1297), Scatter Factor/Hepatocyte Growth Factor (SF/HGF) (Gohji, K., et al., J. Clin. Oncol., 2000; 18:2963-2971), proteins of the keratin/cytokeratin family like cytokeratin 20 (Buchumensky, V., et al., J. Urol., 1998, 160:1971-1974), and cytokeratin 18 (Sánchez-Carbayo, M., et al., Clin. Cancer Res., 2000, 6:3585-3594), Mammary tumour 8-Ka Protein (MAT-8) (Morrison, B.W., et al., J. Biol. Chem., 1995, 270:2176-2182), Telomerase

However, it is likely that many of the genes involved in the initiation and progression of bladder cancer are currently unknown. No marker to predict the prognosis and extent of bladder cancer has been proven useful in clinical trials (Miyake et al., 2002). (Miyake, H., et al., J. Urol., 2002; 167:1282-1287). The identification of differentially expressed genes in bladder cell carcinoma could lead to the identification of biological markers, which could be of significant value for the diagnosis, prognosis and treatment of this disease.

Once transitional cell carcinoma of the bladder has been diagnosed, transurethral resection is carried out to treat superficial papillary tumours; superficial TIS and T1 are treated, in addition to transurethral resection, with intravesicular treatment with Bacillus-Calmette Guerin (BCG). If the cancer is muscle invasive, the patient is treated by radical cystectomy; if the patient will not tolerate this surgery, radiation therapy or chemotherapy is

used. The 69% percent of the patients with muscle invasive TCC die within five years after diagnosis, even after receiving treatment. Alternative therapeutic approaches are necessary to treat muscle invasive TCC with a higher efficiency; also needed are alternative therapeutic approaches to treat low-grade tumours more efficiently than through surgery, or to complement surgery in order to avoid recurrences and progression of the tumour to an invasive state.

Fibroblast growth factors (FGF) are a family of more than twenty proteins involved in the regulation of biological processes including cell proliferation, cell differentiation, cell growth, cell migration, morphogenesis, angiogenesis and tissue remodelling. The FGFs bind with high affinity to cell surface receptors (Fibroblast Growth Factor Receptors, or FGFRs) that have tyrosine kinase activity. The protein kinases are a family of proteins, which effect the phosphorylation of other proteins and play a key role in the regulation of many cellular processes (Hanks, et al., Science 1988, 241, 42-52). When the FGF ligand binds to FGFR, the FGFR is converted to a dimeric active form that autophosphorylates in the kinase domain; then the activated FGFR binds and phosphorylates other effector proteins, thus starting a signal transduction pathway from the cell surface to the nucleus (Crews and Erikson. Cell. 1993. 74:215-217). The loss of regulation of growth factor signalling pathways is a frequent occurrence in cancer.

Four FGFRs have been identified to date: FGFR1 (also called Flg, fms-like gene, flt-2, bFGFR, N- bFGFR or Cek1), FGFR2 (also called Bek –Bacterial Expressed Kinase-, KGFR, Ksam, Ksaml and Cek3), FGFR3 (also called Cek2) and FGFR4. All mature FGFRs share a common structure consisting of an amino terminal signal peptide, three extracellular immunoglobulin-like domains (Ig domain I, Ig domain II, Ig domain III), with an acidic region between Ig domains I and II (the "acidic box" domain), a transmembrane domain, and intracellular kinase domains (Ullrich and Schlessinger, Cell 61:203, 1990; Johnson and Williams (1992) Adv. Cancer Res. 60:1-41). The distinct FGFR isoforms have different binding affinities for the different FGF ligands, thus FGF8 (androgen-induced growth factor) and FGF9 (glial activating factor) appear to have increased selectivity for FGFR3 (Chellaiah et al. J Biol .Chem 1994;269:11620).

Specific point mutations in FGFR3, that lead to the activation of its tyrosine kinase activity, have been previously associated to different syndromes related to bone development (Chen, H., et al. J. Clin. Invest., 1999, 104(11):1517-1525).. Mutations in FGFR3 have also been detected in multiple myelomas (10-25% of tumours. Plowright et al. Blood 2000 Feb 1;95(3):992-8; Chesi et al. Blood 2001 Feb 1;97(3):729-36; Soverini et al. Haematologica 2002 Oct;87(10):1036-40; Pollett et al. Blood 2002 Nov 15;100(10):3819-3821), in cervical carcinomas (3,5-25% of tumours. Sibley et al. Oncogene 2001 Jul

19;20(32):4416-8; Dai et al. Anal Cell Pathol 2001;23(2):45-9) and in bladder carcinomas (Cappellen et al. Nat Genet 1999 Sep;23(1):18-20; Sibley et al. Oncogene 2001 Feb 8;20(6):686-91; Sibley et al. Oncogene 2001 Jul 19;20(32):4416-8; Billerey et al. Am J Pathol. 2001 Jun;158(6):1955-9) Activating FGFR3 mutations were detected in 40-50% of bladder tumours; the incidence was significantly higher, up to 80%, in low grade or superficial tumours than in high grade or invasive tumours; and the bladder cancer recurrence rates were clearly lower for tumours with a mutant FGFR3 (Kimura et al. Cancer 2001 Nov 15;92(10):2555-61; van Rhijn et al. Cancer Res 2001 Feb 15;61(4):1265-8).

Unexpectedly, the authors of the present invention have discovered, after thorough research and using different techniques, that the expression level of the FGFR3 gene and concentration of the protein is elevated in biopsies of bladder transitional cell carcinomas when compared with expression in normal bladder tissue and, moreover, the treatment of bladder cancer cell lines expressing high concentrations of FGFR3 with antibody against FGFR3 protein produce inhibition of cell proliferation of bladder cancer cell lines.

The authors of the present invention have also surprisingly discovered that the elevated levels of FGFR3 protein expression are predominantly associated with superficial tumours.

The present invention, therefore, provides a highly sensitive *in vitro* method to detect the presence of a bladder carcinoma, to determine the stage or severity of this cancer in an individual or to monitor the effect of therapy administered to an individual with the said cancer. Also, the present invention provides targets or tools for the screening, identification, development and evaluation of the efficacy of therapeutic compounds for the treatment of cancer of the bladder, particularly for tumour treatment, as neoadjuvant before resection or as adjuvant after resection with the aim of reducing recurrence and progression. Finally, the invention provides agents characterised by the fact that they inhibit expression and/or activity of the FGFR3 protein for the treatment of cancer of the bladder.

SUMMARY OF THE INVENTION

A first aspect of the present invention is to develop an *in vitro* method to detect the presence of cancer of the bladder, to determine the stage or severity of this cancer in the individual or to monitor the effect of the therapy administered to an individual with this cancer.

A second aspect of the present invention is an *in vitro* method to screen for, identify, develop and evaluate the efficacy of compounds to treat bladder transitional cell carcinoma.

An additional aspect of the invention lies in the use of sequences derived from the FGFR3 gene to establish the diagnosis and prognosis *in vitro* of bladder transitional cell

carcinoma, and to screen for, identify, develop and evaluate the efficacy of compounds for the treatment of this cancer.

A further aspect of the invention consists in the provision of agents that inhibit the expression and /or activity of the FGFR3 protein.

Another aspect of the invention consists of a pharmaceutical composition comprising a therapeutically effective amount of at least one agent that inhibits the expression and /or activity of the FGFR3 protein together with at least one pharmaceutically acceptable excipient.

A final aspect of the present invention consists in a kit for carrying out the present invention.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows results of Western Blot analysis of FGFR3 expression in samples of human bladder. Samples analysed were: Non neoplastic urinary bladder samples: 46, 55 y 63); Low grade superficial transitional cell carcinoma (G1, Ta) samples: 48, 49, 50, 53, 56 and 59; High grade lamina propria infiltrating carcinomas (G3, T1) (samples 57, 61 and 67), High grade muscle infiltrating carcinomas (G3, T2) (samples 47, 51, 58 and 60) and two samples of unknown stage (samples 54 and 62). In all cases 20 micrograms of total protein were loaded. Membranes were incubated with Anti-FGFR3 antibody **(A)** or Anti-actin antibody **(B)**. The analysis showed various immunoreactive bands of different sizes: glycosylated form (135 kDa), the intracellular non-glycosylated form (85 kDa) and several intermediate bands (110-110 kDa) that correspond with different FGFR3 glycosylation states. Smaller immunoreactive bands (50 kDa) were also detected that may have result from proteolytic processing.

Figure 2 shows the results of a western blot analysis of the expression of the FGFR3 protein in the bladder transitional cell carcinoma cell line RT-112. Protein extract of normal bladder tissue was used as control (sample 46). Protein extract from a bladder tumour sample was used as positive control (sample 53). For each sample, a total of 20 micrograms of protein was loaded

Figure 3 shoes the effects of anti-FGFR3 (blue bars) and anti-β2 microglobulin (red bars) on bladder transitional cell carcinoma RT-112 cells growth in serum-free media. Cells were seeded in 96-well plates and were treated with antibodies for 24 or 48 h. Growth rate is expressed a comparison between cell lines growth with and without antibody. Each value is calculated from 6 replicas and the vertical lines represent the standard deviation.

Figure 4 shows tissue array showing circular sections from bladder tissue biopsies after routine staining with hematoxylin and eosin followed by immunohistochemical staining for the FGFR3 protein.

Figure 5 shows immunohistochemical detection of FGFR3 protein in tissue samples of three stages of bladder transitional cell carcinoma, Ta (A and D), T1 (B), T2 (C) and control healthy bladder. Positive staining of FGFR3 was defined as a coarse cytoplasmic membrane reactivity. Immunohistochemistry was considered negative in cases with weak staining of <5% of the cells.

DETAILED DESCRIPTION OF THE INVENTION

To facilitate the comprehension of the present patent application we give the meanings of some terms and expressions in the context of the invention:

The terms "subject" or "individual" refers to all species of animals classified as mammals and includes, but is not restricted to, domestic and farm animals, primates and humans. The subject is preferably a male or female human of any age or race

The term "cancer" refers to the disease that is typically characterised by abnormal or unregulated cell growth, capable of invading adjacent tissues and spreading to distant organs.

The term "carcinoma" refers to the tissue resulting from abnormal or unregulated cell growth.

The term "bladder transitional cell carcinoma" refers to any malign proliferative disorder in bladder epithelial cells.

The term "tumour" refers to any abnormal mass of tissue generated by a neoplastic process, whether this is benign (non cancerous) or malignant (cancerous).

The term "gene" refers to a region of a molecular chain of deoxyribonucleotides that encodes a protein and may represent a portion of a coding sequence or a complete coding sequence.

The term "DNA" refers to deoxyribonucleic acid. A DNA sequence is a sequence of deoxyribonucleotides.

The term "cDNA" refers to a nucleotide sequence complementary to a sequence of mRNA.

The term "RNA" refers to ribonucleic acid. An RNA sequence is a sequence of ribonucleotides.

The term "mRNA" refers to messenger ribonucleic acid, which is the fraction of total RNA, which translates to proteins.

The term "mRNA transcript of" refers to the RNA product transcribed from the corresponding gene (DNA) into mRNA, as a first step in the expression and translation to protein.

The term "nucleotide sequence" or "nucleotidic sequence" refers either to a sequence of ribonucleotides (RNA) or a sequence of deoxyribonucleotides (DNA).

The term "protein" indicates at least one molecular chain of amino acids linked through either covalent or non-covalent bonds. The term includes all forms of post-translational protein modifications, for example glycosylation, phosphorylation or acetylation.

The terms "peptide" and "polypeptide" refer to molecular chains of amino acids that represent a protein fragment. The terms "protein" and "peptide" are used indistinguishably.

The phrase "increased levels" means that the levels measured in patients with bladder cancer are higher than the levels measured in a control population of individuals with no history of bladder transitional cell carcinoma.

The term "specificity", refers to the measurement of false positives, where a specificity of 100% means there are no false positives (positive diagnosis of bladder cancer when the patient individual does not in fact have suffer bladder cancer).

The term "sensitivity", as used herein, refers to the measurement of false negatives, where a sensitivity of 100% means there are no false negatives (negative diagnosis of bladder cancer when the patient in fact does have bladder cancer).

The term "antibody" refers to a glycoprotein that exhibits a specific binding activity for a target molecule called an "antigen". The term "antibody" refers to monoclonal or polyclonal antibodies, either intact or fragments derived from them; and includes human antibodies, humanised antibodies and antibodies of non-human origin. The "monoclonal antibodies" are homogeneous, highly specific antibody populations directed against a single antigenic site or "determinant" of the target molecule. "Polyclonal antibodies" include heterogeneous antibody populations that are directed against different antigenic determinants of the target molecule.

The term "epitope", as it is used in the present invention, refers to an antigenic determinant of a protein, which is the sequence of amino acids of the protein that a specific antibody recognises. Such epitopes may be comprised of a contiguous stretch of amino acids (linear epitope) or of non-contiguous amino acids that are brought into proximity with one another by virtue of the three dimensional folding of the polypeptide chain (discontinuous epitopes).

The term "solid phase", as it is used in the present invention refers to a non-aqueous matrix to which the antibody can bind. Examples of materials for the solid phase include but are not limited to glass, polysaccharides (for example agarose), polyacrylamide,

polystyrene, polyvinylic alcohol and silicons. Examples of solid phase forms are the well of a plate or a purification column.

The terms "oligonucleotide primer" and "primer" are used interchangeably in the present invention, and are used to refer to nucleotide sequences, that are complementary to target nucleotide sequences of the FGFR3 or ribl10 genes. Each primer hybridises with its target nucleotide sequence and acts as an initiation site for nucleotide polymerisation catalysed by DNA polymerase, RNA polymerase or reverse transcriptase.

The term "probe", as it is used in the present invention, refers to a nucleotide sequence complementary to a nucleotide sequence derived from the FGFR3 gene that can be used to detect the corresponding nucleotide sequence derived from the FGFR3 gene.

The term "therapeutic target" refers to nucleotide or peptide sequences against which a drug or therapeutic compound can be designed and clinically applied.

The term "antagonist" refers to any molecule that inhibits the biological activity of the antagonised molecule. Examples of antagonistic molecules include, among others, proteins, peptides, variations of natural peptide sequences and small organic molecules (with a molecular weight usually, but not limited to, less than 500 Daltons).

The present invention is based on the discovery that both gene expression of FGFR3, and the concentration of the FGFR3 protein are increased in bladder transitional cell carcinoma, and that the proliferation of bladder tumour cell lines is inhibited when they are treated with a specific antibody raised against the FGFR3 protein.

Therefore, the present invention first of all provides an *in vitro* method that comprises:

a) the detection and/or quantification of the FGFR3 protein, of the mRNA of the FGFR3 gene, or of the corresponding cDNA in a sample of an individual, and

b) the comparison of the amount of FGFR3 protein, of the mRNA of the *FGFR3* gene or of the corresponding cDNA detected in a sample of an individual, with their normal reference values.

Said in vitro method is employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.

The method provided by the present invention is highly sensitive and specific and is based on the fact that subjects or individuals diagnosed with bladder transitional cell carcinoma, present high levels of mRNA transcribed from the *FGFR3* gene (elevated levels of expression of the *FGFR3* gene) or elevated levels of the protein coded by the *FGFR3*

gene (protein FGFR3), in comparison with the corresponding levels in samples from subjects without a clinical history of this cancer.

The present method comprises a step in which a sample is obtained from the individual. Different liquid samples can be used such as: urine, blood, plasma, serum, pleural fluid, ascitic fluid, synovial fluid, bile, semen, gastric exudate or cerebrospinal fluid. The sample can also consist of bladder that can be obtained by any conventional method, preferably by cystoscopy. Samples can be obtained from subjects previously diagnosed or not diagnosed with transitional cell carcinoma of the bladder; or from a subject receiving treatment, or who has previously received treatment for a cancer, especially for bladder transitional cell carcinoma.

The present method also comprises a step for extraction of the sample, either to obtain an extract of proteins or to obtain an extract of total RNA. One of these two extracts provides the working material for the next phase. The extraction protocols for total protein or total RNA are well known those skilled in the art (Chomczynski P. et al., Anal. Biochem., 1987, 162: 156; Chomczynski P., Biotechniques, 1993, 15: 532). Any conventional assay can be used in the context of the invention to detect a bladder transitional cell carcinoma, provided that it measures *in vitro* the levels of mRNA transcribed from the *FGFR3* gene or its complementary cDNA, or the concentration of the protein FGFR3, in samples collected from individuals to be studied and control individuals.

Therefore, this invention provides a method to detect the presence of a bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual, or to monitor the effect of the therapy administered to an individual who presents this cancer, based either on measuring the levels of the FGFR3 protein or on measuring the level of expression of the *FGFR3* gene.

If the aim is to detect and/or quantify the FGFR3 protein, the method of the invention comprises a first step in which the protein extract of the sample is placed in contact with a composition of one or more specific antibodies against one or more epitopes of the FGFR3 protein and a second step to quantify the complexes formed by antibodies and the FGFR3 protein.

There is a wide range of immunological assays available to detect and quantify formation of specific antigen-antibody complexes; numerous competitive or non-competitive protein-binding assays have been described previously and a large number of these are available commercially. Hence, the FGFR3 protein can be quantified with antibodies such as, for example: monoclonal antibodies, polyclonal antibodies, either intact or recombinant fragments of these, combibodies and Fab or scFv fragments of antibodies, specific for the FGFR3 protein; these antibodies are human, humanised or of animal origin. The antibodies

used in these assays can be labelled or unlabelled; the unlabelled antibodies can be used in agglutination assays; the labelled antibodies can be used in a wide range of assays. Marker molecules that can be used to label antibodies include radionuclides, enzymes, fluorophores, chemoluminescent reagents, enzymatic substrates or cofactors, enzymatic inhibitors, particles, colorants and derivatives. There are a wide variety of assays well known to those skilled in the art that can be used in the present invention, which use unlabelled antibodies (primary antibody) and labelled antibodies (secondary antibodies); these techniques include but are not limited to the western-blot or western transfer, ELISA (Enzyme-Linked immunosorbent assay), RIA (Radioimmunoassay), Competitive EIA (Competitive enzyme immunoassay), DAS-ELISA (Double antibody sandwich-ELISA), immunocytochemical and immunohistochemical techniques, techniques based on the use of biochips or protein microarrays that include specific antibodies or colloidal precipitation in formats such as *dipsticks*. Other ways to detect and quantify the FGFR3 protein include affinity chromatography techniques, ligand binding assays or lectin binding assays. The preferred embodiment of this aspect of the invention is a double antibody sandwich ELISA (*DAS-ELISA*). In this immunoassay any antibody, or combination of antibodies can be used, that are specific against one or more epitopes of the FGFR3 protein. As an example of one of the many possible formats of this assay, a monoclonal or polyclonal antibody, or a fragment of this antibody, or a combination of these antibodies that recognise one or more epitopes of the FGFR3 protein are attached to the surface of a solid phase support and placed in contact with the sample to be analysed and incubated for a specific time and in appropriate conditions to form the antigen-antibody complexes. After washing in appropriate conditions to eliminate non-specific complexes, an indicator reagent, consisting in a monoclonal or polyclonal antibody, or a fragment of this antibody, or a combination of these and which recognises one or more epitopes of the target FGFR3 protein, bound to a signal generating molecule, is incubated with the antigen-antibody complexes in appropriate conditions of time and temperature. The presence of the FGFR3 protein in the sample to be analysed is detected and, if present, quantified and the signal generated is measured. The amount of FGFR3 protein present in the sample to be analysed is proportional to this signal.

When the aim is to detect and/or quantify mRNA or the cDNA corresponding to the *FGFR3* gene and not the protein, the method of the invention to detect the susceptibility of an individual to develop transitional cell carcinoma of the bladder *in vitro* has several different steps. Hence, after obtaining the sample and extracting the total RNA, the method of the invention for the detection of the mRNA or of the corresponding cDNA of the *FGFR3* gene, comprises a first step of amplification of the extract of total RNA or the corresponding cDNA synthesised by reverse transcription from the mRNA and a second step of

quantification of the amplification product of mRNA or of the cDNA of the *FGFR3* gene. One example of mRNA amplification consists in reverse transcription (RT) of the mRNA into cDNA, followed by Polymerase Chain Reaction (PCR), using oligonucleotide primers, using the primer sequences SEQ ID NO.1 and SEQ ID NO. 2. PCR is a technique for the amplification of a specific nucleotide sequence (target) contained in a mixture of nucleotide sequences. In PCR, an excess of a pair of oligonucleotide primers is used that hybridise with complementary strands of the target nucleotide sequence. After this, an enzyme with polymerase activity (DNA Polymerase) extends each primer, using the target nucleotide sequence as a template. The extension products are, therefore, converted into target sequences, after dissociation of the original strand. New primer molecules hybridise and are extended by the polymerase. The cycle is repeated to exponentially increase the number of target sequences. This technique is described in the patents US 4683195 and US 4683202. For detection of *FGFR3* gene expression, total RNA was obtained from transurethral resection biopsies (TURB) from control subjects without transitional cell carcinoma of the bladder and from biopsies of patients that were clinically typed after resection and presented transitional cell carcinoma of the bladder. After Dnasel treatment 1 μg of each RNA sample was reverse transcribed to give first strand cDNA using Superscript II Reverse transcriptase (Invitrogen, Paisley, UK). One microlitre of an 1:40 dilution of this reaction was used for PCR amplification of a 200 bp fragment of the *FGFR3* gene under the following conditions: 25 μl reactions containing 1 μl of 1:40 dilution of cDNA reactions, 3 μl of 6 μM of each primer, 0,5 μl of 10mM dNTPs, 2,5 μl of 10 x PCR buffer, 3 μl of 25 mM $MgCl_2$ and 1 unit of Taq Gold polymerase (Applied Biosystems, Foster City, CA, USA). The amplification conditions used consisted of: 94°C for 10 min (denaturation), followed by 40 cycles of 94°C for 30 sec, 50C for 30 sec, 72°C for 1 min 30 sec, and a final extension at 72°C for 10 min. Many methods have been described previously to detect and quantify amplification products by PCR of which any of these can be used in the present invention. In a preferred method of the invention, the amplified product is detected by agarose gel electrophoresis as follows: five microliters of amplification product are separated by agarose gel electrophoresis at a concentration of 2% agarose, in a Tris-Borate-EDTA (TBE) buffer at 100 volts direct current for one hour. After electrophoresis the gel is stained with ethidium bromide and the amplification product is observed when the gel is illuminated with ultraviolet (uv) light. As an alternative to staining, a preferred method is to transfer the amplified product to a nylon membrane by *Southern blotting or Southern transfer* techniques to be detected with a specific cDNA probe of the FGFR3 gene, appropriately labelled. In another embodiment, mRNA detection is performed following electrophoretic separation of mRNA by transferring the mRNA to a nylon membrane using transfer techniques such as northern-blot or northern

transfer and detecting it with specific RNA probes or of the corresponding cDNA of the *FGFR3* gene. In one specific embodiment of this aspect of the invention, amplification and quantification of the mRNA corresponding to the *FGFR3* gene, is carried out by quantitative RT-PCR in real time (Q-PCR).

The final step of the method of the invention to detect *in vitro* the presence of the cancer in a sample from an individual comprises comparing the amount of protein FGFR3, the amount of mRNA of the *FGFR3* gene or the amount of the corresponding cDNA, detected in a sample of an individual, with the amount of protein FGFR3, the amount of mRNA of the *FGFR3* gene, the amount of corresponding cDNA, detected in the samples of control subjects or in previous non-tumorous samples of the same individual or with normal reference values.

In another aspect, the invention also provides a method *in vitro* to identify and evaluate the efficacy of therapeutic agents against bladder transitional cell carcinoma that comprises:

a) placing into contact a culture of bladder tumour cells, with the candidate compound, in the appropriate conditions and for the time required for these to interact,

b) detection and quantification of the expression levels of the *FGFR3* gene or the FGFR3 protein or both, and

c) comparing these expression levels with those of a control culture of tumour cells not treated with the candidate compound.

Quantification of the expression levels of the *FGFR3* gene or the FGFR3 protein is performed in a similar manner to that described in the method of the invention to detect *in vitro* the presence of a cancer of the pancreas, especially of a bladder transitional cell carcinoma, in an individual.

When an agent reduces the expression levels of the *FGFR3* gene or reverses the effects of high expression of this gene, preferably reducing the levels of cellular proliferation, this agent becomes a candidate for cancer therapy, in particular for bladder transitional call carcinoma.

Another aspect of this invention refers to the use of nucleotide or peptide sequences derived from the *FGFR3* gene, in methods to screen for, identify, develop and evaluate the efficacy of therapeutic compounds against bladder transitional cell carcinoma. It is noteworthy, the recent importance given to screening methods based on the competitive or non-competitive binding of the potential therapeutic molecule to the therapeutic target.

A further aspect of this invention refers to the use of nucleotide or peptide sequences derived from the *FGFR3* gene to detect the presence of a carcinoma, especially

of a bladder transitional cell carcinoma, to determine the stage or severity of this cancer in the individual or to monitor the effect of the therapy administered to an individual with this cancer.

Another aspect of this invention consists in providing agents which inhibit expression and/or activity of the FGFR3 protein. These agents, which can be identified and evaluated according to the present invention, can be selected from the group formed by:

a) an antibody, or combination of antibodies, specific against one or more epitopes present in the FGFR3 protein, preferably a human or humanised monoclonal antibody. These can also be a fragment of antibody, a single chain antibody or an anti-videotape antibody,

b) cytotoxic agents, such as toxins, molecules with radioactive atoms or chemotherapeutic agents, including, but not limited to, small organic and inorganic molecules, peptides, phosphopeptides, antisense molecules, ribozymes, siRNAs, triple helix molecules etc. that inhibit expression and/or activity of the FGFR3 protein, and

c) compounds that are antagonists of the FGFR3 protein, that inhibit one or more of the functions of the FGFR3 protein

A further aspect of the present invention is a pharmaceutical composition that includes a therapeutically effective amount of one or several of the previously mentioned agents together with one or more excipients and/or transporter substances. Also, this composition can contain any other active ingredient that inhibits the function of the FGFR3 protein. The excipients, transporter compounds and auxiliary substances must be pharmaceutically and pharmacologically tolerated so that they can be combined with other components of the formulation or preparation and not have any adverse effects on the organism treated. The pharmaceutical compositions or formulations include those that are suitable for oral or parenteral administration (including subcutaneous, intradermal, intramuscular or intravenous), although the best route of administration depends on the patient's condition. Formulations can also be in the form of single doses. Formulations are prepared according to well known pharmacological methods. The amounts of active substances to be administered vary depending on the characteristics of the therapy.

A final aspect of the present invention consists in a kit for carrying out the present invention. Thus, an embodiment of the present invention provides a kit that comprises an anti-FGFR3 antibody and a carrier in suitable packing. In another embodiment the kit of the invention comprises a primer pair designed to specifically amplify a nucleic acid having a sequence that is specific of the *FGFR3* gene. The sequence of the primer pair can be

determined from the sequence of the corresponding *FGFR3* gene by employing bioinformatic tools. The sequence of said primer pair is preferably selected from SEQ ID NO.1 and SEQ ID NO.2. These kits can be employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.

The following examples serve to illustrate the invention.

Example 1.- Differential analysis of the expression of the FGFR3 gene in samples of bladder tissue, using *Human Genome U95 DNA arrays*

1.1. Materials and methods

Microarrays. GeneChip Test 3 (Affymetrix, Santa Clara) microarrays were used, that permit the quality of RNA to be tested before analysing expression with the GeneChip Human Genome U95A array (Affymetrix, Santa Clara), which represents 12,000 complete sequences of annotated genes; the FGFR3 gene is represented in the microarray by the set of probes **31805_at** of Affymetrix, which are sense oligonucleotides 25 nucleotides long, designed on the basis of the Hs.1420 sequence of Unigene, or **N. Acc. M64347** of GeneBank (Table 1).

Table 1. Description of the probes corresponding to the set of probes 31805_at.

Consecutive order of probes	Region of the interrogated reference sequence	Probe sequence (5'-3')	Probe position in mRNA sequence
1	3511	SEQ ID NO: 3	3227
2	3625	SEQ ID NO: 4	3340
3	3633	SEQ ID NO: 5	3348
4	3663	SEQ ID NO: 6	3378
5	3684	SEQ ID NO: 7	3399
6	3716	SEQ ID NO: 8	3431
7	3722	SEQ ID NO: 9	3437
8	3821	SEQ ID NO: 10	3536
9	3825	SEQ ID NO: 11	3540
10	3831	SEQ ID NO: 12	3546
11	3861	SEQ ID NO: 13	3576
12	3873	SEQ ID NO: 14	3588
13	3891	SEQ ID NO: 15	3606
14	3903	SEQ ID NO: 16	3618
15	3933	SEQ ID NO: 17	3648
16	4005	SEQ ID NO: 18	3720

Samples

The samples studied were from transurethral resection biopsies (TURB) from control non-neoplastic individuals (7 cases, 2 containing muscular layer and 5 without muscular layer) and from biopsies of patients that were clinically typed after resection and presented transitional cell bladder carcinoma (22 cases) in one of the following stages: Nine cases were low-grade non-invasive carcinomas (pTaG1), seven cases were high-grade carcinomas with lamina propria invasion (pT1G3), and six cases were high-grade muscle invading carcinomas (pT2G3). Every sample was histologically typed (grade and stage) in the Pathological Anatomy Department of the University Hospital Marques de Valdecilla, the same hospital where the samples were obtained following the guidelines of the Helsinki Declaration. Fresh tissue was immediately frozen in liquid nitrogen after extraction and stored at –80°C until processing.

For each stage of tumour the following samples were analysed:

- Control tissue without muscular layer; 5 samples
- Control tissue with muscular layer: 2 samples
- TaG1: 9 samples
- T1G3: 7 samples
- T2G3: 6 samples

***GeneChip* gene expression analysis**

Analysis was done with total RNA from individual subjects and with equimolar mixtures (pools) of total RNAs from either healthy individuals or from patients suffering the same stage of bladder transitional cell carcinoma. (Table 2).

Table 2. Description and number of samples comprised in each pool

	Epithelial Control	Muscular Control	Ta G1	T1 G3	T2 G3
Samples	3*(pC1)[a], 2 (pC3)	2 (pC2)	1,4(pTa.1)[b], 4 (pTa.2)	1,2(pT1.1)[c], 4 (pT1.2)	1, 2(pT2.1)[d], 3 (pT2.2)

* number of samples comprising each pool.
[a] pC: *pool* of control sample. Example: 3(pC1) = *pool* 1 with 3 control samples.
[b] pTa: *pool* of Ta tumour samples. Example: 4(pTa.1) = *pool* 1 with 4 TaG1 samples.
[c] pT1: *pool* of T1 tumour samples. Example: 2(pT1.1) = *pool* 1 with 2 T1G3 samples.
[d] pT2: *pool* of T2 tumour samples. Example: 2(pT2.1) = *pool* 1 with 2 T2G3 samples.

cRNA synthesis

Total RNA from each biopsy was obtained by homogenising the tissue in TRIzol® Reagent (Life Technologies), following the supplier's recommendations. The resulting total

RNA was cleaned with the Rneasy kit (QIAGEN) (Chomczynski P. et al., Anal. Biochem., 1987, 162: 156; Chomczynski P., Biotechniques, 1993, 15: 532). Of each preparation of total RNA, 10 µg were used as starting material for synthesis of the first strand cDNA with the reverse transcriptase enzyme SuperScript™ II RNase (Life Technologies), using as a primer an oligo-dT oligonucleotide carrying the T7 phage RNA polymerase promoter sequence. Second strand cDNA was synthesised using the enzymes DNA polymerase I of *E. coli* (Invitrogen Life Technologies), DNA ligase of *E. coli* (Invitrogen Life Technologies), RNAse H of *E. coli* (Invitrogen Life Technologies), and DNA polymerase of phage T4 (Invitrogen Life Technologies). The biotin labelled cRNA was synthesised using the ENZO BioArray™ HighYield™ Transcript Labelling Kit (Enzo Diagnostics Inc). After *in vitro* transcription, the unincorporated nucleotides were eliminated using the RNeasy columns (QIAGEN).

Array Hybridization and scanning

A total of 15 µg of each biotinylated cRNA were fragmented at 94°C for 35 minutes in a buffer solution containing 40 mM Tris-Acetate (pH 8.1), 100 mM potassium acetate and 30 mM magnesium acetate. The fragmented cRNA was mixed with hybridization buffer (100 mM MES, 1M NaCl, 20 mM EDTA, 0.01% Tween 20) and heated to 99° for 5 minutes and then to 45° for 5 minutes, after which it was loaded in the Affymetrix array. The first array in which the hybridization was carried out was Test 3 of Affymetrix. With this array the quality of RNA can be tested before analysing expression in the Affymetrix® GeneChip® *Human Genome* 95 A (HG-U95A).

For hybridization, arrays were incubated in a rotary incubator at 45° for 16 hours with a constant rotation of 60 rpm.

Washing and staining of each array was done in the Affymetrix® fluid station. A washing and staining programme was used that included:

- 10 x 2 washing cycles with SSPE-T 6x (0.9 m NaCl, 60 mM NaH_2PO4, 6 mM EDTA, 0.01% Tween 20) at 25°C,
- 4x15 cycles with 0.1 mM MES, 0.1M NaCl, 0.01% Tween 20 at 50°C,
- Staining with biotinylated cRNA with a phycoerythrin streptavidin conjugate (10 µg/ml Molecular Probes)
- 10 x 4 washing cycles with SSPE-T at 25C°
- Staining an anti-streptavidin conjugate for 10 minutes
- Staining a phycoerythrin-streptavidin conjugate (1 mg/ml, Molecular Probes) for 10 minutes
- 15 x 4 washing cycles with SSPE-T at 30C°

Arrays were scanned at 560 nm using a confocal microscope that uses laser emission (Agilent GeneArray Scanner). Analysis of intensity readings was done with the Microarray Suite 5.0 software. For comparison of arrays these were scaled to a total intensity of 100.

1.2. Results

Analysis of differential expression of the *FGFR* 3 gene in neoplastic samples compared to controls was performed from the Affymetrix microarray data. The following parameters were considered in the analysis: detection (classification of the gene as; present (P), absent (A) or marginal (M), in each sample); Change (indicating an increase (I), decrease (D) or no change (NC) for each sample); and the Signal Log Ratio (SLR; indicating the change in expression levels between a base line control and each sample). This change is expressed as the $\log_2$ of the ratio (base 2 logarithm of the *fold change* or

number of times that gene expression, is increased or decreased in the tumour sample compared to the non neoplastic control sample). We considered a SLR of 1 or –1 (representing respectively a fold change increase or decrease of 2) as a significant value for gene expression change

Compared to controls expression levels of *FGFR3* were increased more than 8-fold (SLR>3) in pTaG1 and pT1G3 carcinomas and more than 4–fold (SLR>2) in T2G3 carcinomas (Table 3).

Table 3. Microarray hybridization results for Fibroblast growth factor receptor 3 (FGFR3) based on Affymetrix MAS5.0 software. (N. Acc. M64347)

Control sample signal	Control sample detection	Detection pTaG1 stage	SLR TaG1 vs Control	TaG1 Change	Comparison
132.7	P	P	2.5	I	pTa.1 vs pC1
67.7	A	P	4.2	I	pTa.1 vs pC2
28.1	A	P	4.4	I	pTa.1 vs pC3
132.7	P	P	1	I	pTa.2 vs pC1
67.7	A	P	3	I	pTa.2 vs pC2
28.1	A	P	3.5	I	pTa.2 vs pC3
SLR Average			**3.1**		
Control sample signal	**Control sample detection**	**Detection G3 stage**	**SLR T1G3 vs. Control**	**T1G3 Change**	**Comparison**
132.7	P	P	1.7	I	pT1.1 vs. pC1
67.7	A	P	3.9	I	pT1.1 vs. pC2
28.1	A	P	3.7	I	pT1.1 vs. pC3
132.7	P	P	2	I	pT1.2 vs. pC1
67.7	A	P	4.1	I	pT1.2 vs. pC2
28.1	A	P	4.4	I	pT1.2 vs. pC3
SLR Average			**3.3**		
Control sample signal	**Control sample detection**	**Detection T2 G3 stage**	**SLR T2G3 vs Control**	**T2G3 Change**	**Comparison**
132.7	P	P	1.4	I	pT2.1vspC1
67.7	A	P	3.3	I	pT2.1vspC2
28.1	A	P	3.2	I	pT2.1vspC3
132.7	P	P	0.6	I	pT2.2vspC1
67.7	A	P	2.4	I	pT2.2vspC2
28.1	A	P	2.7	I	pT2.2vspC3
SLR Average			**2.26**		

1.3. Discussion

Differential expression analysis of FGFR3 gene confirmed that compared to controls expression levels of *fgfr3* were increased more than 8-fold (SLR>3) in pTaG1 and pT1G3 carcinomas and more than 4–fold (SLR>2) in T2G3 carcinomas (Table 3).

Example 2.- Differential analysis of expression of the FGFR3 protein in bladder tissue samples using the western blot technique with specific antibodies.

2.1. Materials and Methods

Samples:

Samples were obtained form transurethral resection biopsies (TURB). In this part of the study we analysed three urinary bladder samples from healthy individuals (samples 46, 55 and 63), six low-grade superficial carcinomas (pTaG1) (samples 48, 49, 50, 53, 56 and 59), three high-grade lamina propria invasive carcinomas (pT1G3) (samples 57, 61 and 67) four high-grade muscle-invading carcinomas (pT2G3) (samples 47, 51, 58 and 60) and two samples of unknown grade (samples 54 and 62). The samples were from different patients than those used for the microarray analysis. Fresh tissue was immediately frozen in liquid nitrogen after extraction and stored at –80ºC until used for extraction of protein. All the samples used in this study were obtained by surgical transurethral resection performed in the Urology Service of the University Hospital Marques de Valdecilla (Santander, Spain); samples were histologically typed in the Anatomical Pathology department of the same hospital. The precepts of the Helsinki Declaration were followed throughout.

Protein extraction

The frozen tissue samples were homogenised in mortars with liquid nitrogen and the pulverized product was added to RIPA B buffer (sodium phosphate 20 mM [pH 7,4], NaCl 150 mM, Triton X-100 1%, EDTA 5 mM) as well as a proteases inhibitor cocktail (Roche Diagnostics Inc., Mannheim, Germany).

Western blotting experiments

Protein samples (20 μg of total protein) were mixed with SDS-PAGE gel loading buffer supplemented with 5% β-mercaptoethanol and incubated at 100ºC for 5 min, before being loaded on 6% polyacrylamide gel. Following electrophoresis proteins were transferred to nitrocellulose membranes. Duplicate gels were run and blotted. One membrane was probed with antibodies raised against the FGFR3 protein (Santa Cruz Biotech. Inc., Santa

Cruz, CA, USA.) while the second membrane was probed with antibody raised against actin (Amersham, Little Chalfont, UK) as a control for protein loading. Finally, membranes were hybridised with a secondary antibody conjugated with peroxidase (Amersham) and the chemoluminescent signal was detected using the ECL system (Amersham) with high performance chemiluminescence film (Hyperfilm ECL, Amersham).

2.2. Results.

Expression of the FGFR3 protein in bladder transitional cell carcinoma

FGFR3 protein expression in healthy samples (n = 3) and tumours (n = 15) was investigated by western blotting. The results are shown in figure 1 and table 4. As the results show the *FGFR3* protein was not detected in the control samples analysed. With regard to the tumour samples FGFR3 was present in 11 of the 15 samples analysed (73%), being higher in low-grade tumours (83%) and high-grade tumours that infiltrated the lamina propria (100%).

The receptor appeared in the form of several immunoreactive bands of distinct molecular weights: Western blot analysis showed bands forming a smear of glycosylated form 135 kDa, corresponding to the fully glycosylated form; 85 kDa corresponding to the intracellular non-glycosylated form and several bands of intermediate molecular weight corresponding with the different FGFR3 glycosylation states In addition some low molecular weight (50 kDa) immunoreactive bands were also present, which may represent proteolytic degradation products of the protein (Figure 1).

Table 4: FGFR-3 protein expression.

Sample	*N*	Samples positive for FGFR3	% 0f samples positive
normal bladder	3	0	0
TaG1	6	5	5 (83%)
T1G3 Carcinoma	3	3	3 (100%)
T2G3 Carcinoma	4	2	2 (50%)
Unclassified	2	1	2 (100%)

2.3. Discussion

The results obtained shown that the FGFR3 protein, which is undetectable in normal bladder tissue is expressed in the majority of the bladder transitional cell carcinoma samples. In some these tumours the level of FGFR3 protein is singularly high. The sensitivity of the detection system is 73% with 100% specificity.

Example 3. In vitro inhibition of bladder tumoral cell line proliferation by specific antibodies against the FGFR3 protein.

3.1. Materials and Methods

Culture cell lines:

The RT112 human bladder carcinoma epithelial cell line was obtained from the German Collection of Microorganisms and Cell Cultures (Braunschweig, RFA). RT-112 cells were grown in RPMI medium, supplemented with 10% foetal bovine serum (FBS) and 2 mM glutamine, except where otherwise stated. Tissue culture reagents were obtained from Invitrogen (Paisley, UK).

Preparation of Protein Lysates:

Cells from a 10 cm plate were washed twice with cold phosphate buffered saline (PBS), pH 7.4 and collected in 0,5 ml of RIPA B. Samples were centrifuged at 15000 x g for 10 min at 4°C to pellet cellular debris. The supernatant was kept and the protein concentration was measured using the Bradford protein assay (BioRad, Hercules, CA, USA) (Molina, M. A. et al., Cancer Res., 1999, 59: 4356-4362).

Protein samples (20 μg of total protein) were mixed with SDS-PAGE gel loading buffer supplemented with 5% of β-mercaptoethanol and incubated at 100°C for 5 min, before being loaded on 6% polyacrylamide gel. Following electrophoresis proteins were transferred to nitrocellulose membranes. Duplicate gels were run and blotted. One membrane was probed with antibodies raised against the FGFR3 protein (Santa Cruz Biotech. Inc., Santa Cruz, CA, USA) while the second membrane was probed with an antibody raised against actin (Amersham) as a control for protein loading. Finally, membranes were hybridised with a secondary antibody conjugated with peroxidase (Amersham, Little Chalfont, UK) and the chemoluminescent signal was detected using the ECL system (Amersham) with high performance chemiluminescence film (Hyperfilm ECL,

Amersham).

Cell Proliferation Assays:

Experiments were performed to evaluate the effect of a mouse monoclonal antibody raised against human FGFR3 on the proliferation of RT-112 cells by comparing the proliferation rate of cells grown in the presence of the antibody raised against FGFR3 with proliferation in the presence of a control antibody raised against mouse β2-microglobulin (Santa Cruz). The preservative sodium azide was first removed from the antibody solutions by washing and concentrating the antibodies three times with PBS using a 10-kDa Centricon filtration device (10-kDa MWCO, Millipore CO., Bedford, MA), followed by filter sterilization through a 0.2 µm filter previously saturated with Dulbecco's modified Eagle's medium (DMEM) and 10% FBS. Antibodies were diluted in culture media. RT-112 cells were seeded in a 96-well plate at a density of $2x10^3$ cells per well (0,2 ml) in RPMI medium containing 10% foetal bovine serum (FBS). Cells were allowed to attach to the wells for 24 hours before the RPMI medium was removed and replaced by fresh RPMI containing antibodies at concentrations of: 0, 0.02, 0.2, 2 and 20 µg/ml. The growth rate was estimated after 24 and 48 hours by measuring the formation of reduced MTT (methylthiazoltetrazolium) (Sigma Chemical Co., St Louis, USA) Briefly, after 1 and 2 days incubation, media was removed and replaced by 100 µl of 1 mg/ml MTT in RPMI medium containing 10% FBS. To provide the blanks for absorbance readings some control wells of medium alone were included. The plate was incubated for 30 to 60 minutes at 37°C. After the media was removed, 100 µl of DMSO were added to each well. The cells viability was determined by MTT absorbance (550 nm) and extrapolation of the absorbance intensity from a standard curve.

3.2. Results.

Expression of FGFR3 protein in the bladder transitional cell carcinoma cell line RT-112:

Expression of FGFR3 was tested by western blot analysis, detecting high levels of the receptor (Figure 2). This appeared in the form of various immunoreactive bands of different molecular weights: 135 kDa corresponding to the fully glycosylated form; 85 kDa corresponding to the intracellular non-glycosylated form and several intermediate bands (100-110 kDa) corresponding to different FGFR3 glycosylation states. In addition lower molecular weight (50 kDa) immunoreactive bands were detected possibly corresponding to proteolytic degradation of the protein.

Inhibition of cell Growth by antibodies against FGFR3:

During recent years many antibodies have been described that are directed against extracellular domains of membrane receptors that posses antiproliferative properties. For this reason it was decided to test whether a monoclonal antibody, raised against FGFR3, was capable of inhibiting the growth of a bladder transitional cell carcinoma cell line. For the assay the cell line RT-112 was selected as the only cell line showing detectable levels of the receptor. Assays were performed in serum free media or in media supplemented with 10% foetal bovine serum and cells were incubated for 24 and 48 hours in the presence of antibody for 24 and 48 hours. As a control another monoclonal antibody, obtained from the same source (Santa Cruz Biotechnology) and raised in mice against β2 microglobulin was used As shown in figure 3, anti-FGFR3 antibody inhibited proliferation of RT-112 cells in serum free-media after 48 hours while anti-β2 microglobulin antibody showed no effect. On the other hand, in 10% FBS supplemented media, none of the antibodies showed a significant effect on proliferation of RT-112 cells.

3.3. Discussion

The results presented in this example show that the expression level of the FGFR3 protein, which is not detectable in normal bladder, is elevated in the bladder carcinoma cell line RT-112. FGFR3 is a membrane glycoprotein that interacts with the FGF family of growth factors triggering a signalling cascade that stimulates cell proliferation (Keegan et al., Oncogene, 1991, 6:2229-2236). This receptor could play a pivotal role in the origin and progression of bladder transitional cell carcinoma.

Treatment of RT-112 cell with a monoclonal antibody directed against the extracellular domain of FGFR3 protein in serum-free media, inhibits cell growth. Different, and not mutually exclusive mechanisms, could explain this effect: the antibody could block receptor binding, or inhibit receptor dimerisation (the step prior to receptor activation), or deplete the concentration of receptor at the plasma membrane.

To summarise, the over-expression of FGFR3 in bladder transitional cell carcinoma and the fact that proliferation of the bladder carcinoma cell line RT-112 is inhibited by a monoclonal antibody raised against FGFR3, suggests that this protein is a promising candidate as a therapeutic target for the development of drugs to treat bladder transitional cell carcinoma; likewise these results show that the antibody against FGFR3 protein could be the active ingredient of one of the drugs developed.

Example 4. Analysis of protein expression in tissue samples using tissue arrays

4.1. Material and Methods

Fixed paraffin-embedded tumour samples from the pathology archives of the Hospital Universitario Marqués de Valdecilla were sectioned and arrayed on glass slides. In total 209 cases of urinary bladder transitional cell carcinoma from transurethral resection biopsies and cystectomy specimens and 20 healthy bladder samples (total: 229) were examined by immunohistochemical staining. All paraffin-embedded donor tissue blocks were sampled with 0.6-mm punchers using a Beecher tissue microarray instrument (Beecher Instruments Inc. Sun Prairie, WI, USA). Paraffin tissue array blocks containing arrayed core cylinders from 37 pTa, 100 pT1, 72 pT2 and 20 healthy bladder samples were subjected to routine staining with hematoxylin and eosin followed by immunohistochemical staining for the FGFR3 protein. A monoclonal antibody raised against FGFR3 (1:25 dilution; Santa Cruz Biotech. Inc., Santa Cruz, CA, USA) was used for immunostaining.

Briefly, antigen retrieval was performed by boiling sections in citric acid buffer in a pressure cooker for 90 sec. The Dako EnVisionTM + kit (Dako, Glostrup Denmark) was used as a visualization system according to the manufacturers' instructions, in a Techmate 500-220 automated immunostainer (Biotek, Santa Barbara, CA, USA). Diaminobenzidine was used as the chromogen (figure 4).

To reduce interobserver variability in the histopathological evaluation of the antibody-stained specimens three independent pathologists from the Pathological Anatomy Department of the University Hospital Marques de Valdecilla evaluated staining patterns and scoring criteria were agreed. Positive staining of FGFR3 was defined as a coarse cytoplasmic membrane reactivity (figure 5). Immunohistochemistry was considered negative in cases where staining was absent or which showed weak staining (<5% of cells in a given section).

4.2. Results

Of the urinary bladder transitional cell carcinoma sections that were analysed immunohistochemically a positive reaction with the antibody specific for FGFR3 was positive in 71.4% of Ta sections, 72% of T1 sections and 49.2% of T2 sections (table 5) compared to the 5 % of healthy positive sample. Consistent with previous data the T1 sections

classified as high-grade showed a lower percentage of positive sections (table 6) than sections corresponding to lower grades of transitional cell carcinoma of the bladder.

Table 5. Description of samples analysed and tissue array results

Bladder transitional cell carcinoma pT1 grade	Total nº of sections	Useable sections	Positive cases	Negative cases	Null ca	% of positive cases
G1	16	15	15		1	**100 %**
G2	32	31	24	8	3	**77.4 %**
G3	24	22	13	10	1	**59.1%**

* Cases that have not been analysed due to the array preparation
** Percentage of positive cases among useable sections

Table 6. Results of Immunohistochemical Staining

	Total nº of samples	Useable sections	Positive cases	Negative cases	Null cas	% of positive cases**
Bladder transitional cell carcinoma pTa	37	36	25	11	1	**71.4 %**
Bladder transitional cell carcinoma pT1	100	93	67	26	7	**72 %**
Bladder transitional cell carcinoma pT2	72	67	33	34	5	**49.2%**
Bladder Healthy tissue	20	20	1	19	-	**5%**

* Cases that have not been able to be analysed due to the array preparation
** Percentage of positive cases among useable sections

4.3. Discussion

The results presented in this example provide evidence for FGFR3 protein expression in a large number of bladder cancer transitional cell carcinomas (209). Elevated levels of FGFR3 protein expression in cell membranes was predominantly associated with the Ta and T1 stages (mainly superficial tumours) of bladder cancer transitional cell carcinomas. Percentages of positive Ta, T1 and T2 cases correlate well with previous results obtained in western blot analysis of FGFR3 expression in bladder cancer transitional cell carcinoma biopsy samples.

CLAIMS

1. An *in vitro* method that comprises:

a) the detection and/or quantification of the FGFR3 protein, of the mRNA of the *FGFR3* gene, or of the corresponding cDNA in a sample of an individual, and

b) the comparison of the amount of FGFR3 protein, of the mRNA of the *FGFR3* gene or of the corresponding cDNA detected in a sample of an individual, with their normal reference values.

2. An *in vitro* method according to claim 1 which is employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.

3. Method according to claims 1 and 2 in which the sample to be analysed is a sample of bladder tissue.

4. Method according to claim 3 in which the sample of bladder tissue is obtained by any conventional method, preferably by cystoscopy.

5. Method according to claims 1 and 2 in which the sample to be analysed is a sample of urine, blood, plasma, pleural fluid, ascitic fluid, synovial fluid, bile, semen or cerebrospinal fluid.

6. Method according to claims 1 and 2 in which the sample to be analysed is obtained from an individual not previously diagnosed with bladder transitional cell carcinoma.

7. Method according to claims 1 and 2 in which the sample to be analysed is obtained from an individual who has been previously diagnosed with bladder transitional cell carcinoma.

8. Method according to claims 1 and 2 in which the sample to be analysed is obtained from an individual receiving treatment, or who has been treated previously against bladder transitional cell carcinoma.

9. Method according to claims 1 and 2 characterised in that it comprises the extraction of the sample, either to obtain an extract of proteins or an extract of total RNA.

10. Method according to claim 1 characterised in that the detection and/or quantification of the FGFR3 protein comprises a first step, in which the protein extract of the sample is placed in contact with a composition of one or more specific antibodies, against one or more epitopes of the FGFR3 protein, and a second step, in which the complexes formed by the antibodies and the FGFR3 protein are quantified.

11. Method according to claim 10, characterised in that said antibodies correspond to monoclonal or polyclonal antibodies, intact or recombinant fragments of antibodies, combibodies and Fab or scFv antibody fragments, specific against the FGFR3 protein; these antibodies being human, humanised or of non-human origin.

12. Method according to claims 10 or 11 characterised in that in the detection and/or quantification of the complexes formed by antibodies and the FGFR3 protein, the techniques used are selected from the group comprised by: western-blot, ELISA (Enzyme-Linked Immunosorbent assay), RIA (Radioimmunoassay), Competitive EIA (Competitive Enzyme Immunoassay), DAS-ELISA (Double Antibody Sandwich-ELISA), immunocytochemical or immunohistochemical techniques, techniques based on the use of biochips or protein microarrays that include specific antibodies, assays based on the precipitation of colloidal gold in formats such as dipsticks; or by affinity chromatography techniques, ligand binding assays or lectin binding assays.

13. Method according to claim 1 characterised in that the detection and/or quantification either of the mRNA or of the corresponding cDNA of the *FGFR3* gene, comprises a first step of amplification of the mRNA that is present in the extract of total RNA, or of the corresponding cDNA synthesised by reverse transcription of the mRNA; and a second step of quantification of the amplification product from either the mRNA or the cDNA of the *FGFR3* gene.

14. Method according to claim 13 characterised in that the amplification is performed qualitatively or quantitatively, by RT-PCR using primer oligonucleotides, where the sequences of the primers used to amplify the sequence of the *FGFR3* gene are SEQ ID NO.1 and SEQ ID NO.2.

15. Method according to claim 1 characterised in that the detection and/or quantification is done with specific probes either of mRNA or of the corresponding cDNA of the *FGFR3* gene, by techniques such as northern-blot or northern transfer.

16. Method according to claim 1 characterised in that the detection and/or quantification of the mRNA is done by Real time quantitative RT-PCR (Q-PCR).

17. Use of nucleotide or peptide sequences derived from the *FGFR3* gene, to detect *in vitro* the presence of a bladder transitional cell carcinoma, to determine *in vitro* the stage or severity of this cancer in the individual, or to monitor *in vitro* the effect of the therapy administered to an individual with this cancer.

18. An *in vitro* method to identify and evaluate the efficacy of therapeutic compounds against cancer bladder transitional cell carcinoma that comprises:

a) placing in contact a culture of bladder tumour cells (with uncontrolled proliferation) with the candidate compound, in the appropriate conditions and for a suitable time for these to interact,

b) detect and/or quantifying expression levels of the *FGFR3* gene or the FGFR3 protein, and

c) compare said expression levels with those of the control cultures of tumour cells not treated with the candidate compound.

19. Use of a nucleotide or peptide sequence derived from the *FGFR3* gene, in methods to screen for, identify, develop and evaluate the efficiency of compounds to bladder transitional cell carcinoma.

20. An agent that inhibits the expression and/or activity of the FGFR3 protein.

21. An agent according to claim 20 selected from the group formed by:

a) an antibody, or combination of antibodies, specific against one or more epitopes present in the FGFR3 protein, preferably a human or humanised monoclonal antibody; a fragment of an antibody, a single chain antibody or an anti-idiotype antibody,

b) cytotoxic agents such as toxins, molecules with radioactive atoms or chemotherapeutic agents, including small organic and inorganic molecules, peptides, phosphopeptides, antisense molecules, ribozymes, triple helix

molecules, double stranded RNA etc., which inhibit expression and/or activity of the FGFR3 protein and

c) antagonistic compounds of the FGFR3 protein, which inhibit one or more of the functions of the FGFR3 protein.

22. Agent according to claims 20 or 21 to treat a cancer of the bladder transitional cell carcinoma.

23. Use of any of the agents according to claims 20 or 21 in the manufacturing of a medicinal product for the treatment of bladder transitional cell carcinoma.

24. Pharmaceutical composition comprising a therapeutically effective amount of at least one agent according to claims 20 or 21 and at least one pharmaceutically acceptable excipient.

25. Pharmaceutical composition according to claim 24 that characterised because it contains further active ingredients, preferably one that inhibits the function of the FGFR3 protein.

26. A kit that comprises an antibody that specifically recognises the FGFR3 protein and a carrier in suitable packaging

27. A kit that comprises a primer pair designed to specifically amplify a nucleic acid having a sequence that is specific to the *FGFR3* gene.

28. A kit according to claim 27 wherein the sequence of the primer pair is selected from SEQ ID NO.1 and SEQ ID NO. 2.

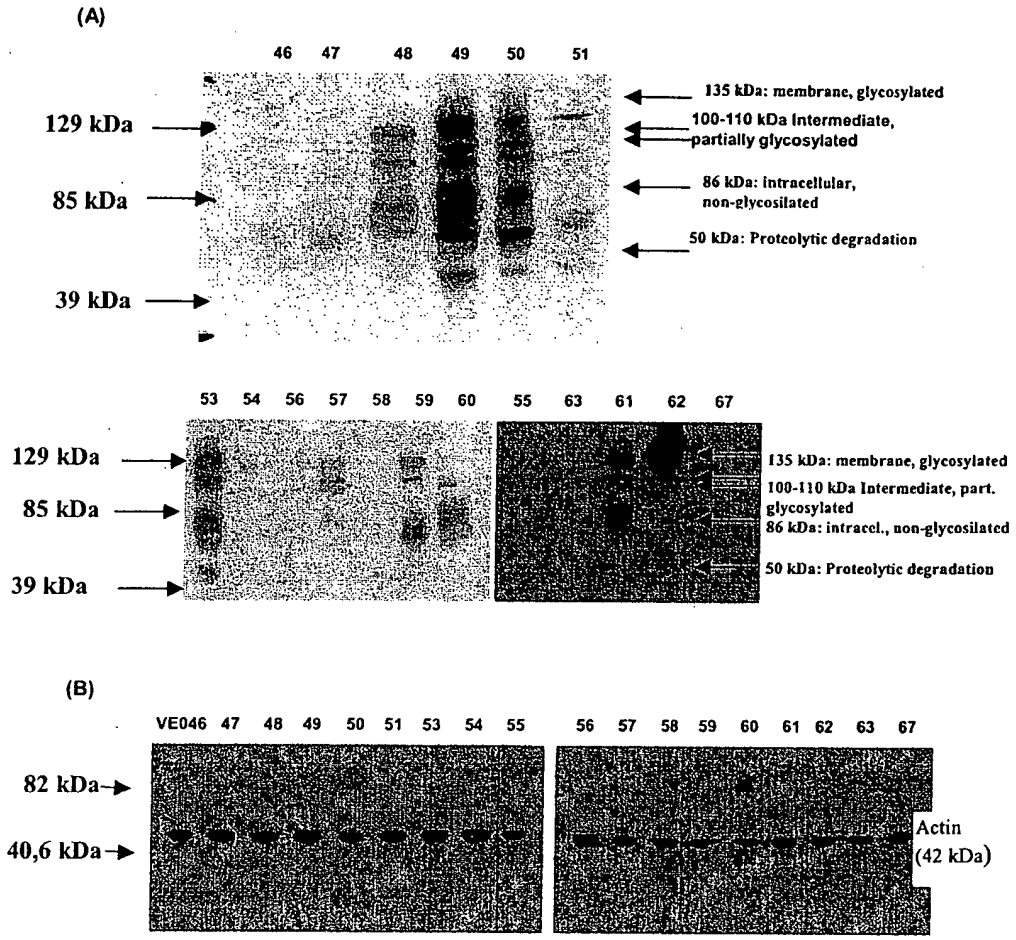
29. A kit according to claims 26 to 28 that is employed to detect the presence of the bladder transitional cell carcinoma in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of the therapy administered to the individual with this cancer.

ABSTRACT

IN VITRO METHOD TO DETECT CARCINOMA BLADDER TRANSITIONAL CELL CARCINOMA

The present invention refers to an *in vitro* method to detect a bladder transitional cell carcinoma, in an individual, to determine the stage or severity of this cancer in an individual or to monitor the effect of therapy administered to an individual with this cancer; to screen for, identify, develop and evaluate the efficacy of therapeutic compounds against this cancer in order to develop new medicinal products, and also agents that inhibit the expression and/or activity of the FGFR3 protein and/or the effects of this expression.

Figure 1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85 kDa
39 kDa
135 kDa: membrane, glycosylated
100-110 kDa Intermediate, partially glycosylated
86 kDa: intracellular, non-glycosilated
50 kDa: Proteolytic degradation
53 54 56 57 58 59 60 55 63 61 62 67
129 kDa
85 kDa
39 kDa
135 kDa: membrane, glycosylated
100-110 kDa Intermediate, part. glycosylated
86 kDa: intracel., non-glycosilated
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(42 kDa)

Figure 2

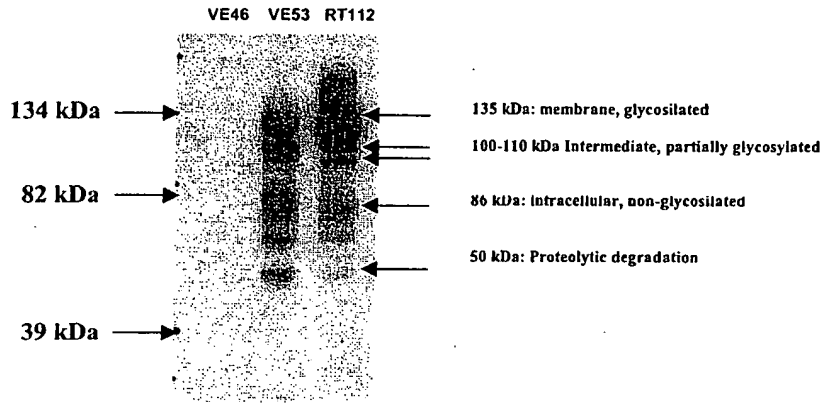
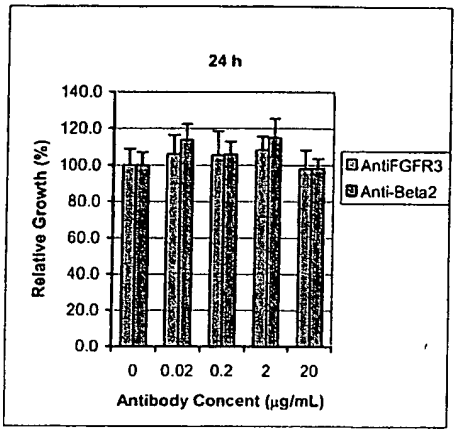

VE46 VE53 RT112
134 kDa
82 kDa
39 kDa
135 kDa: membrane, glycosilated
100-110 kDa Intermediate, partially glycosylated
86 kDa: intracellular, non-glycosilated
50 kDa: Proteolytic degradation

Figure 3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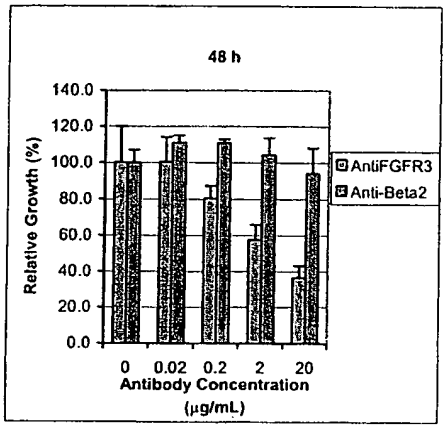
Antibody Concent (µg/mL)
AntiFGFR3
Anti-Beta2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60.0
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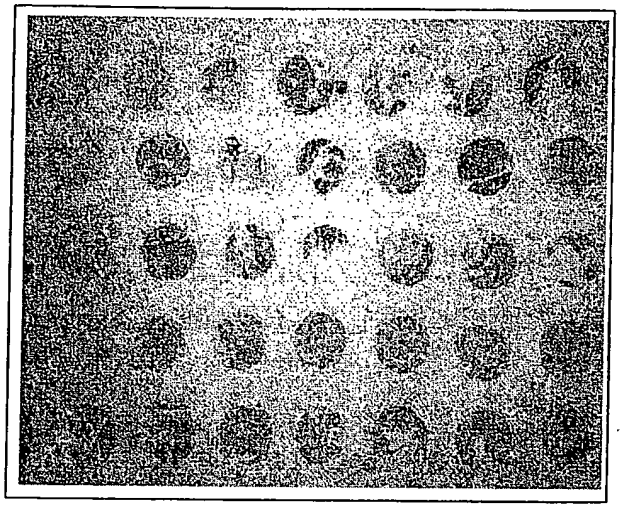
AntiFGFR3
Anti-Beta2

Figure 4



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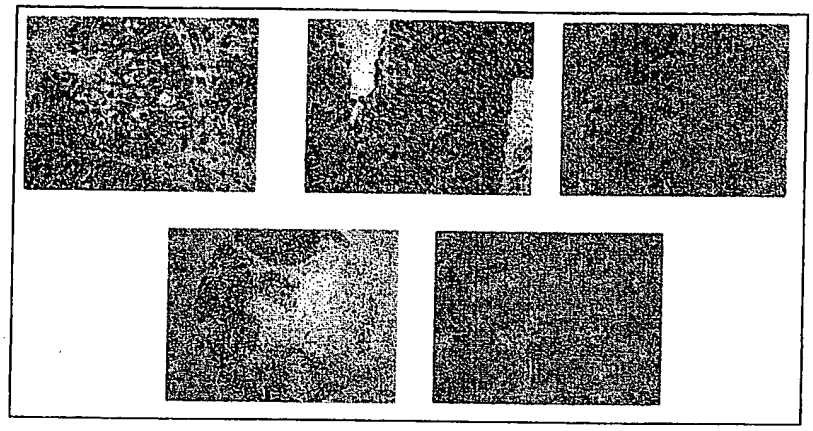

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<223> probe sequence of the 31805_at probe set of Affymetrix, the position of said probe in the mRNA sequence of the fgfr3 gene being 3648

<400> 17
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<210> 18
<211> 25
<212> DNA
<213> Artificial sequence

<220> synthetic DNA
<223> probe sequence of the 31805_at probe set of Affymetrix, the position of said probe in the mRNA sequence of the fgfr3 gene being 3720

<400> 18
gtggccagag gtgtcaccca aaccg 25

Beatriz Rodera [ABG PATENTES]

De: Andreas Baltatzis [abaltatzis@krameramado.com]
Enviado: miércoles, 08 de marzo de 2006 19:00
Para: brodera@abgpatentes.com
CC: Arlir Amado
Asunto: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008

Dear Beatriz

I work with Arlir Amado, who is out this week. He has asked me to review the file for your reference no. P1121USPC. It appears that a diligent effort has been made to reach the non-signing inventor. We recommend one final attempt to contact the inventor by sending an email that includes the declaration, assignment and a copy of the application itself.

In order to prepare the statement of facts necessary to petition to file without a joint inventor, we will require the following information:

1. The Inventor's last known mailing address to which the documentation was originally sent by the Applicant.
2. The name of the person who will be signing the document, preferably the person at ABG Patentes who has been trying to contact Mr. Molina
3. Copies of all the email correspondence between the Applicant, ABG and Mr. Molina.

Once we have received this information we will prepare the statement of facts and petition required by 37 CFR § 1.47.

With regards to the assignment, we note that a decision granting a petition under 37 CFR § 1.47 does not alter the ownership interest or title of the application. If the nonsigning inventor has not signed as assignment document which has been recorded in the USPTO, then the 37 CFR 1.47 Applicant is NOT the assignee of the entire interest of the application. However, the Applicant will have the ability to conduct the prosecution of the application as a partial assignee where one of the inventors has refused to join and a petition under 37 CFR. § 1.47 has been granted.

Please feel free to contact me with any questions. Arlir will be back in the office on March 13th.

Best regards,
Andreas

Andreas Baltatzis
Associate
KRAMER & AMADO, P.C.
Direct 703.519.9806
Main 703.519.9801
Fax 703.519.9802
E-Mail: abaltatzis@krameramado.com
www.krameramado.com

****
*** REPORTE DE TX ***
****

TRANSMISIÓN OK

N° TRABAJO	3618
DIRECCIÓN DESTINO	00017035199802
CLAVE/SUBDIR	
ID CONEXIÓN	KRAMER & AMADO
HORA COM.	03/03 14:31
TP USADO	00'25
PÁGS.	2
RESULTADO	OK

abg
patentes
ARIAS , BERNARDO & GONZÁLEZ
Asesoría y Agencia de la Propiedad Industrial
Intellectual Property

KRAMER & AMADO, P.C.
1725 Duke Street, Suite 240
Alexandria, Virginia 22314
United States

Atn.:Arlir Amado

Via Facsimile
Confirmation by mail

Our ref.: P1121USPC
Your ref.: ABG 3008

Madrid, March 3, 2006

Re: **Patent Application in United States No. 10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA", in the name of PROGENIKA BIOPHARMA, S.A.**

Dear Sirs,

Further to your mail dated January 31, 2006, please be informed that in order to get the signature of the inventor (Miguel Angel Molina), the following steps have been performed:

- First of all, the Applicant sent the documentation two or three times to the last known address of the inventor, but there was no answer. Then, the applicant tried to locate him per "yellow pages" of the Spanish Telephone Company, but there was no input under his name.

- Afterwards, ABG Patentes got the e-mail address of the inventor by change (through an indirect personal contact)

patentes
ARIAS , BERNARDO & GONZÁLEZ
Asesoría y Agencia de la Propiedad Industrial
Intellectual Property

KRAMER & AMADO, P.C.
1725 Duke Street, Suite 240
Alexandria, Virginia 22314
United States

Atn.:Arlir Amado

Via Facsimile
Confirmation by mail

Our ref.: P1121USPC
Your ref.: ABG 3008

Madrid, March 3, 2006

Re: Patent Application in United States No. 10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA", in the name of PROGENIKA BIOPHARMA, S.A.

Dear Sirs,

Further to your mail dated January 31, 2006, please be informed that in order to get the signature of the inventor (Miguel Angel Molina), the following steps have been performed:

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- Afterwards, ABG Patentes got the e-mail address of the inventor by chance (through an indirect personal contact).

- On February 7, 2005, ABG Patentes sent Miguel Angel Molina via e-mail the documents of "Assignment" and "Declaration and Power of Attorney". He answered to this e-mail asking how is the better way to return us these documents once signed. We answered this question thinking that he was ready to cooperate.

- On February 8, 2006, he wrote again asking whether it was possible to change the address of the document of "Declaration and Power of Attorney" to his home address and, also, that if the signature of the document of "Assignment" meant to loose his rights over this patent application.

- On February 9, 2006, we answered to his questions saying that we would change his address in the document of "Declaration and Power of Attorney", and that if he signed the document he would loose indeed, any kind of rights over the patent. We continued by saying that according to the Spanish Patent Law, and according to the contract he signed with the Applicant, the inventions made during his stay in the company are considered to belong to the company he works or worked for.

- After our last e-mail (February 9, 2006), we sent him two reminders about this matter, one on February 15, 2006 and the other one on February 20, 2006, but the inventor has not answered yet. Moreover, we believe the inventor will never answer back. Unfortunately, we could only get his e-mail address, not his home or work address.

This is the present situation for this case. Therefore, we would appreciate if you could inform us what would be the following step with respect to the filing of the Assignment" and "Declaration and Power of Attorney" before the USPTO

Best regards,

Juan Arias Sanz
European Patent Attorney
ABG Patentes, S.L.

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: miércoles, 01 de marzo de 2006 18:28
Para: 'Laureano Simon'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: RV: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008
Importancia: Alta

Estimado Laureano:

Le reenviamos el e-mail que hemos escrito a nuestros agentes explicándoles la situación de este caso, ya que Miguel Ángel Molina no ha vuelto a responder a nuestros e-mails.

Un saludo,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Beatriz Rodera [ABG PATENTES] [mailto:brodera@abgpatentes.com]
Enviado el: miércoles, 01 de marzo de 2006 18:22
Para: 'Arlir Amado'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: RE: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008
Importancia: Alta

Dear Sirs,

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This is the present situation for this case. Therefore, we would appreciate if you could inform us what would be the following step with respect to the filing of the Assignment" and "Declaration and Power of Attorney" before the USPTO

Best regards,

Beatriz Rodera Tobal
Formalities Department

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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Arlir Amado [mailto:arlir@kramerip.com]
Enviado el: martes, 31 de enero de 2006 17:16
Para: Beatriz Rodera [ABG PATENTES]
Asunto: RE: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008

Dear Beatriz:

I apologize for my delay. I've responded to your email directly below your questions. Let me know if these steps have been taken so we can move forward and prepare a statement of facts. If you can get back to me with a draft a statement, we'll then modify and return to you for review.

Regards,
Arly

O/Ref.: P1121USPC
Y/Ref.: AGB 3008

Re.: Patent Application in United States No.10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMA, S.A.

Dear Sirs:

This is in connection with your e-mail dated October 17, 2005, regarding the Declaration and Power of Attorney Form.

The Applicant has had problems in obtaining the signature of all of the inventors. Actually, the Applicant and one of the inventors had serious discussion and, as a consequence, the inventor no longer works for the Applicant and, further, he does not want to sign the Declaration and Power of Attorney Form.

The Applicant has sent us all the documentation regarding the several times he has sent the Form to the inventor.

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: miércoles, 01 de marzo de 2006 18:22
Para: 'Arlir Amado'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: RE: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008
Importancia: Alta

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Best regards,

Beatriz Rodera Tobal
Formalities Department

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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Arlir Amado [mailto:arlir@kramerip.com]
Enviado el: martes, 31 de enero de 2006 17:16
Para: Beatriz Rodera [ABG PATENTES]
Asunto: RE: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008

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Regards,
Arly

O/Ref.: P1121USPC
Y/Ref.: AGB 3008

Re.: Patent Application in United States No.10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMA, S.A.

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The Applicant has sent us all the documentation regarding the several times he has sent the Form to the inventor.

We believe that you might need a report from the applicant answering the following questions to prepare and affidavit to be filed before the USPTO:

What were the circumstances of the refusal? When there is an express oral refusal, that fact along with the time and place of the refusal must be stated in the statement of facts. When there is an

express written refusal, a copy of the document evidencing that refusal must be made part of the statement of facts. The document may be redacted to remove material not related to the inventor's

reasons for refusal. Statements by a party not present when an oral refusal is made will not be accepted. MPEP 409.03(d).

(1) How do we know the address of the non-signing inventor and what steps were taken to verify that the address to which the declaration was sent is actually the correct address? What documentation is available to prove this? (e.g., printouts of recent internet searches, telephone directories, updated human resource records). I would try to obtain confirmation of the inventor's address and telephone number using a resource such as Ultimate White Pages; the MPEP only specifies that it is necessary to send the papers to the "last known address," so if basic internet searches confirm the most recent human resource records, this should be sufficient.

(2) What steps were taken by you to contact the non-signing inventor? (Here, you would describe how you mailed the declarations to the non-signing inventor's address three times, and the corresponding results of these mailing.) Also, it would be extremely useful if you searched for the telephone number of the non-signing inventor and tried to call him. A copy of the application papers should be sent to the last known address of the nonsigning inventor, or, if the nonsigning inventor is represented by counsel, to the address of the nonsigning inventor's attorney. MPEP 409.03(d).

(3) For each action taken, what documentation can be provided to show that the step was actually done? In the case of the mailings, we already have the certified mail return receipts and the cover letters that you provided. As mentioned above, other helpful evidence would be printouts of internet searches to determine the telephone and/or address of the non-signing inventors. Copies of documentary evidence such as internet searches, certified mail return receipts, cover letters of instructions, telegrams, that support a finding that the nonsigning inventor could not be found or reached should be made part of the statement. The steps taken to locate the whereabouts of the nonsigning inventor should be included in the statement of facts. MPEP 409.03(d).

From: Beatriz Rodera [ABG PATENTES] [mailto:brodera@abgpatentes.com]
Sent: Tuesday, January 31, 2006 3:21 AM
To: Arlir Amado; Rusty Belicek
Subject: RV: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008
Importance: High

REMINDER

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
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28020 Madrid
(SPAIN)

Tel.: +34 91 417 13(
Fax: +34 91 417 13(
brodera@abgpatentes.co
http://www.abgpatentes.co

-----Mensaje original-----
De: Beatriz Rodera [ABG PATENTES] [mailto:brodera@abgpatentes.com]
Enviado el: martes, 17 de enero de 2006 13:52
Para: 'aamado@kramerip.com'
Asunto: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008
Importancia: Alta

O/Ref.: P1121USPC
Y/Ref.: AGB 3008

Re.: Patent Application in United States No.10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMA, S.A.

Dear Sirs:

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The Applicant has sent us all the documentation regarding the several times he has sent the Form to the inventor.

We believe that you might need a report from the applicant answering the following questions to prepare and affidavit to be filed before the USPTO:

(1) How do we know the address of the non-signing inventor and what steps were taken to verify that the address to which the declaration was sent is actually the correct address? What documentation is available to prove this? (e.g., printouts of recent internet searches, telephone directories, updated human resource records).

(2) What steps were taken by you to contact the non-signing inventor? (Here, you would describe how you mailed the declarations to the non-signing inventor's address three times, and the corresponding results of these mailing.) Also, it would be extremely useful if you searched for the telephone number of the non-signing inventor and tried to call him.

(3) For each action taken, what documentation can be provided to show that the step was actually done? In the case of the mailings, we already have the certified mail return receipts and the cover letters that you provided. As mentioned above, other helpful evidence would be printouts of internet searches to determine the telephone and/or address of the non-signing inventors.

Could you please confirm me you need this information and, if necessary, which further information and documents are needed?

Very truly yours

Beatriz Rodera Tobal
Formalities Department

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Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 13(
Fax: +34 91 417 13(
brodera@abgpatentes.co
http://www.abgpatentes.co

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: lunes, 20 de febrero de 2006 17:47
Para: 'Miguel Molina'
CC: Juan Arias (jarias@abgpatentes.com); 'Laureano Simon'
Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Estaríamos muy agradecidos nos comunicara su decisión sobre la firma de los documentos de "Assignment" y "Declaration and Power of Attorney" de la solicitud de patente en Estados Unidos.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Beatriz Rodera [ABG PATENTES] [mailto:brodera@abgpatentes.com]
Enviado el: miércoles, 15 de febrero de 2006 18:01
Para: 'Miguel Molina'
CC: 'Laureano Simon'; 'Juan Arias'
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Le recordamos que estamos a la espera de que nos comunique su decisión sobre la firma de los documentos de "Assignment" y "Declaration and Power of Attorney" enviados con fecha 7 de febrero de 2006.

En espera de sus noticias le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Juan Arias [mailto:jarias@abgpatentes.com]
Enviado el: jueves, 09 de febrero de 2006 15:30
Para: 'Miguel Molina'
CC: 'Laureano Simon'; 'Beatriz Rodera [ABG PATENTES]'
Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Como respuesta a su e-mail de ayer le comentamos lo siguiente:

- Respecto a la dirección, no habría ningún problema en poner su dirección actual ya que como bien dice no usted es trabajador de Progenika Biopharma, S.L.

- En relación a la pregunta que nos hacía sobre la firma del documento de "Assignment", efectivamente la firma implica la renuncia a cualquier derecho sobre la invención. No obstante, cuando Vd. comenzó a trabajar en la empresa, firmó una renuncia a cualquier derecho sobre la propiedad intelectual derivada del trabajo que realizara dentro de la misma, tanto en su contrato de trabajo como en un documento de renuncia a favor de Proteomika, S.L. Le adjuntamos copia de ambos documentos.

  Por otro lado, tal y como establece la **Ley de Patentes (11/1986)**, las invenciones realizadas por el trabajador durante su contrato pertenecerán a la empresa y el inventor debe prestar su colaboración para la efectividad de los derechos del Título.

  Articulo 15.1 de la Ley de Patentes (11/1986) "*Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario*"
  Articulo 18.2 de la Ley de Patentes (11/1986) "*Tanto el empresario como el trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos*"

Esperamos que esta información le sirva de ayuda.

En espera de su decisión, le saluda atentamente,

Juan Arias Sanz
Partner
M.Sc. (Chemistry)
Spanish Patent Agent / European Patent Attorney

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
jarias@abgpatentes.com
http://www.abgpatentes.com

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: miércoles, 15 de febrero de 2006 18:01
Para: 'Miguel Molina'
CC: 'Laureano Simon'; 'Juan Arias'
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Le recordamos que estamos a la espera de que nos comunique su decisión sobre la firma de los documentos de "Assignment" y "Declaration and Power of Attorney" enviados con fecha 7 de febrero de 2006.

En espera de sus noticias le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Juan Arias [mailto:jarias@abgpatentes.com]
Enviado el: jueves, 09 de febrero de 2006 15:30
Para: 'Miguel Molina'
CC: 'Laureano Simon'; 'Beatriz Rodera [ABG PATENTES]'
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- Respecto a la dirección, no habría ningún problema en poner su dirección actual ya que como bien dice no usted es trabajador de Progenika Biopharma, S.L.

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  Por otro lado, tal y como establece la **Ley de Patentes (11/1986)**, las invenciones realizadas por el trabajador durante su contrato pertenecerán a la empresa y el inventor debe prestar su colaboración para la efectividad de los derechos del Título.

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  Articulo 18.2 de la Ley de Patentes (11/1986) "*Tanto el empresario como el*

trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos"

Esperamos que esta información le sirva de ayuda.

En espera de su decisión, le saluda atentamente,

Juan Arias Sanz
Partner
M.Sc. (Chemistry)
Spanish Patent Agent / European Patent Attorney

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28020 Madrid
(SPAIN)

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jarias@abgpatentes.com
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Beatriz Rodera [ABG PATENTES]

De: Juan Arias [jarias@abgpatentes.com]
Enviado: jueves, 09 de febrero de 2006 15:30
Para: 'Miguel Molina'
CC: 'Laureano Simon'; 'Beatriz Rodera [ABG PATENTES]'
Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Como respuesta a su e-mail de ayer le comentamos lo siguiente:

- Respecto a la dirección, no habría ningún problema en poner su dirección actual ya que como bien dice no usted es trabajador de Progenika Biopharma, S.L.

- En relación a la pregunta que nos hacía sobre la firma del documento de "Assignment", efectivamente la firma implica la renuncia a cualquier derecho sobre la invención. No obstante, cuando Vd. comenzó a trabajar en la empresa, firmó una renuncia a cualquier derecho sobre la propiedad intelectual derivada del trabajo que realizara dentro de la misma, tanto en su contrato de trabajo como en un documento de renuncia a favor de Proteomika, S.L. Le adjuntamos copia de ambos documentos.

  Por otro lado, tal y como establece la **Ley de Patentes (11/1986)**, las invenciones realizadas por el trabajador durante su contrato pertenecerán a la empresa y el inventor debe prestar su colaboración para la efectividad de los derechos del Título.

  Articulo 15.1 de la Ley de Patentes (11/1986) "*Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario*"
  Articulo 18.2 de la Ley de Patentes (11/1986) "*Tanto el empresario como el trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos*"

Esperamos que esta información le sirva de ayuda.

En espera de su decisión, le saluda atentamente,

Juan Arias Sanz
Partner
M.Sc. (Chemistry)
Spanish Patent Agent / European Patent Attorney

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Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

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Fax: +34 91 417 1301
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http://www.abgpatentes.com

CONTRATO DE TRABAJO DE DURACION DETERMINADA

MINISTERIO DE TRABAJO
Y ASUNTOS SOCIALES
Instituto Nacional de Empleo

OFICINA DE EMPLEO
GETXO
Sello de registro del Servicio Público de Empleo
27 MAY 2003
ESTA DILIGENCIA NO SUPONE PRONUNCIAMIENTO SOBRE EL CONTENIDO DEL DOCUMENTO

Código de contrato

- [X] Tiempo completo:
  - [X] Obra o Servicio Determinado — 4 0 1
  - [ ] Eventual por circunstancias de la producción — 4 0 2
  - [ ] Interinidad — 4 1 0
- [ ] Tiempo Parcial:
  - [ ] Obra o Servicio Determinado — 5 0 1
  - [ ] Eventual por circunstancias de la producción — 5 0 2
  - [ ] Interinidad — 5 1 0
- [ ] Situación jubilación parcial — 5 4 0

DATOS DE LA EMPRESA

CIF/NIF B62793526

D/Dª Antonio Martinéz Martinéz

Nombre o Razón Social de la Empresa: PROTEOMIKA, S.L.
NIF/NIE: 27460766P
En concepto (1): Apoderado
Domicilio Social: JOSEP SAMITIER, 1-5
País:
Municipio: 0 8 0 2 8
C. Postal: 0 8 0 2 8

DATOS DE LA CUENTA DE COTIZACION

Régimen: 0 1 1 1
Cod.prov.: 0 8
Número: 1370200
Dig.contr.: 0 4
Actividad Económica: Inv.Cient. y Tec. Co

DATOS DEL CENTRO DE TRABAJO

País:
Municipio:

DATOS DEL/DE LA TRABAJADOR/A

D/Dª MIGUEL MOLINA VILA
NIF/NIE: 33895291F
Fecha de nacimiento: 02-03-65
Nº afiliación a la S.S.: 081008741563
Nivel formativo: DOCTORADO
Nacionalidad:
Municipio del domicilio:
País domicilio:

Con la asistencia legal, en su caso, de D/Dª .....
N.I.F/NIE....., en calidad de (2) .....

DECLARAN

Que reúnen los requisitos exigidos para la celebración del presente contrato y, en consecuencia acuerdan formalizarlo con arreglo a las siguientes:

CLAUSULAS

Primera: La persona contratada prestará sus servicios como (3) .....Investigador..... en el grupo profesional/categoría/nivel (4) .....Investigadora..... incluido en sistema de clasificación profesional vigente en la empresa.

Segunda: La jornada de trabajo será (5):

- [X] **A tiempo Completo:** la jornada de trabajo será de .....40..... horas semanales, prestadas de .....Lunes..... a .....Viernes..... con los descansos que establece la Ley.
- [ ] **A tiempo Parcial:** la jornada de trabajo ordinaria será de .....horas : Al día [ ] A la semana [ ] Al mes [ ] Al año [ ] , siendo esta jornada inferior a (6):
  - [ ] La de un trabajador a tiempo completo comparable.
  - [ ] La jornada a tiempo completo prevista en el Convenio Colectivo de aplicación.
  - [ ] La jornada máxima legal.

  La distribución del tiempo de trabajo será
  .....
  .....

(1) Directora, Gerente, etc.
(2) Padre, madre, tutor/a o persona o institución que le/la tenga a su cargo.
(3) Indicar profesión.
(4) Señalar el grupo profesional y la categoría o nivel profesional que corresponda, según el sistema de clasificación profesional vigente en la empresa.
(5) Marque con una X lo que corresponda
(6) Marque con una X la situación que corresponda

PE/177

Tercera: La duración del presente contrato se extenderá desde 27-05-03 hasta 26-05-04
Se establece un periodo de prueba de (7) S/ Estatuto Trabajadores
En caso de que el convenio colectivo permita una duración mayor a la establecida legalmente, señálelo con una X: ☐

Cuarta: El/la trabajador/a percibirá una retribución total de 28550 euros brutos (8) Anuales
que se distribuye en los siguientes conceptos salariales (9) Salario Base y Plus COnvenio
En el supuesto del contrato para sustituir a trabajadores en formación por trabajadores beneficiarios de prestaciones por desempleo, el trabajador desempleado contratado percibirá la prestación contributiva o el subsidio por desempleo a que tenga derecho. El ompresario durante el período de percepción de la prestación o subsidio que se compatibiliza, deberá abonar al trabajador la diferencia entre la cuantía de la prestación o subsidio por desempleo y el salario que le corresponde, siendo asimismo responsable de la totalidad de las cotizaciones a la Seguridad Social por todas las contingencias y por el total del salario indicado incluyendo el importe de la prestación o el subsidio.

Quinta : Las vacaciones anuales serán de (10) 30 días naturales (Prop. al tiempo trabajado)

Sexta : El contrato de duración determinada se celebra para:

☒ La realización de la obra o servicio (11) Identificación de mamarcadores en cancer de vejiga, teniendo dicha obra autonomía y sustantividad propia dentro de la actividad de la empresa.

☐ Atender las exigencias circunstanciales del mercado, acumulación de tareas o exceso de pedidos, consistentes en .....(12), aún tratándose de la actividad normal de la empresa. En caso de que se concierte por un plazo inferior a la duración máxima legal o convencionalmente establecida podrá prorrogarse, mediante acuerdo de las partes, por una única vez, sin que la duración total del contrato pueda exceder de dicha duración máxima.

☐ Sustituir al trabajador ..... (13), siendo la causa:

- ☐ Sustituir a trabajadores con derecho a reserva del puesto de trabajo
- ☐ Sustituir a trabajadoras por maternidad, sin bonificación de cuotas.
- ☐ Sustituir a trabajadores excedentes por cuidado de familiares, siendo el trabajador que sustituye al excedente, perceptor, durante más de un año, de prestaciones por desempleo de nivel contributivo o asistencial (Disposición Adicional 14ª del Real Decreto Legislativo 1/95).
- ☐ Para cubrir temporalmente un puesto de trabajo durante el proceso de selección o promoción, para su cobertura definitiva.
- ☐ Sustituir a trabajadores en formación por trabajadores beneficiarios de prestaciones por desempleo (14). Se acompaña certificado expedido por la Administración Pública o entidad encargada de gestionar la formación.

El trabajador contratado desempeñará el puesto de trabajo de ..... (15).

☐ Reducir la jornada de trabajo y el salario en un ..... (16), cuando el trabajador reúna las condiciones generales exigidas para tener derecho a la pensión contributiva de jubilación de la Seguridad Social, con excepción de la edad, que habrá de ser inferior, como máximo, cinco años a la exigida, o cuando, reuniendo las citadas condiciones generales, hayan cumplido ya dicha edad.

Séptima: A la finalización del contrato, excepto en los casos de contrato de interinidad, el trabajador tendrá derecho a recibir una indemnización de cuantía equivalente a la parte proporcional de la cantidad que resultaría de abonar ocho días de salario por cada año de servicio, o la establecida, en su caso, en la normativa específica que sea de aplicación.

Octava: El presente contrato se regulará por lo dispuesto en la legislación vigente que resulte de aplicación y particularmente por los artículos 12 y 15 del Estatuto de los Trabajadores, por la Ley 12/2001 de 9 de julio (B.O.E. de 10 de julio), y Real Decreto 2.720/1998, de 18 de diciembre (B.O.E. de 8 de enero) y en su caso, por lo establecido en la Disposición transitoria sexta del R.D.Ley 5/2002, de 24 de mayo (B.O.E. de 25 de mayo), por el que se desarrolla el citado art. 15 del Estatuto de los Trabajadores. Asimismo le será de aplicación lo dispuesto en el Convenio Colectivo de Quimicas

Novena: El contenido del presente contrato se comunicará al Servicio Público de Empleo de ....., en el plazo de los 10 días siguientes a su concertación.

Décima: Ambas partes se comprometen a comunicar el fin de la relación laboral a los Servicios Públicos de Empleo cuando ésta se produzca, de conformidad con lo establecido en el artículo 42.3 de la Ley 51/1980, de 8 de octubre, Básica de Empleo.

CLÁUSULAS ADICIONALES

" El trabajador renuncia a cualquier derecho sobre la propiedad intelectual derivado del trabajo a desarrollar en la Mercantil contratante"

Y para que conste, se extiende este contrato por triplicado ejemplar, en el lugar y fecha a continuación indicados, firmando las partes interesadas.
En Barcelona a 27 de Mayo de 20 03

El/la trabajador/a

El/la representante de la empresa

El/la representante legal del/de la menor, si procede
NO REPRESENTANTE SINDICAL

(7) Respetando lo establecido en el artículo 14.1 del Texto Refundidos de la Ley del Estatuto de los Trabajadores, aprobado por el Real Decreto Legislativo 1/1995, de 24 de marzo.
(8) Diarios, semanales o mensuales.
(9) Salario base y complementos salariales
(10) Mínimo: 30 días naturales.
(11) Identifique con claridad la obra o servicio, con autonomía y sustantividad propia dentro de la actividad de la empresa en la que prestara servicio el trabajador contratado
(12) Indíquese la causa o circunstancia que justifique la realización del contrato.
(13) Indíquese el nombre del trabajador sustituido.
(14) Solo para empresas de hasta 100 trabajadores y siempre que tales acciones formativas estén financiadas por cualquiera de las Administraciones Públicas (Art. 1do laDisposición transitoria sexta del R.D.Ley 5/2002.
(15) Indicar el el puesto de trabajo a desempeñar será el del/de la trabajador/a o del otro/a trabajador/a de la empresa que pase a desempeñar el puesto de aquel/aquella. Igualmente deberá identificarse, en su caso, el puesto de trabajo cuya cobertura definitiva se producirá tras el proceso de selección externa o promoción interna.
(16) Indicar el porcentaje de reducción de la jornada y del salario,éste será entre un 25 y un 85%.

ACUERDO MUTUO DE CONFIDENCIALIDAD

El presente **ACUERDO DE CONFIDENCIALIDAD** (en adelante "Acuerdo") se formaliza a 27 de mayo de 2002.

REUNIDOS

1. De una parte **Laureano Simón Buela,** con D.N.I. 35308166, Consejero Delegado de **PROTEOMIKA, S.L.** con domicilio a estos efectos en Joseph Samitier, 1-5, 08028 Barcelona, Barcelona, y C.I.F. B62793526 (en adelante "Proteomika ")

2. De otra parte, **Miguel Ángel Molina Vila** con D.N.I. 33895291F con domicilio en Barcelona (en adelante "el trabajador").

EXPONEN

1. Que PROTEOMIKA posee tanto información y tecnología confidencial relacionada con sus proyectos de I+D y los contratados por sus clientes como información relacionada con el negocio de PROTEOMIKA y sus empresas afiliadas incluyendo sin carácter limitativo, todos los datos comerciales y financieros así como también información relacionada de alguna forma.

2. Que el trabajador ha sido contratado por la Empresa como Investigador con fecha 27 de Mayo de 2002

3. Que para la realización normal del trabajo, PROTEOMIKA va a revelar Información al trabajador en los términos y condiciones que se especifican en este acuerdo.

ACUERDAN

1. **Interpretación**

El objetivo del presente acuerdo:

"Información de PROTEOMIKA": Incluye toda información propiedad de PROTEOMIKA sea cual sea su naturaleza, que dicha entidad considere que, por alguna ú otra razón, no deba trascender a personas distintas de aquellas a quienes vaya estrictamente dirigida, incluyéndose en tal definición cualquier información, documentación y/o metodología desarrollada y/o elaborada por Proteomika desde su constitución así como la desarrollada y/o elaborada por las partes durante la vigencia del Contrato de Trabajo del Trabajador en la empresa.

2. **Compromisos**

PROTEOMIKA se compromete:

1. a revelar al trabajador toda la información necesaria para la normal realización de las tareas relacionadas con su puesto de trabajo en la empresa.

El Trabajador se compromete:

1. a utilizar toda la Información propiedad de PROTEOMIKA única y exclusivamente con el objeto de realizar las tareas necesarias para el normal desempeño de su trabajo en la empresa;

2. a mantener la confidencialidad de la Información propiedad de PROTEOMIKA a la que tenga acceso sea cual sea la forma por la que el mismo haya tenido conocimiento de dicha información; y

3. a devolver, todos los documentos y demás material en posesión custodia o control del trabajador, que contengan o incorporen parte de la Información propiedad de PROTEOMIKA, una vez que el trabajador deje de estar contratado por la empresa.

De conformidad con las obligaciones anteriores, el Trabajador no utilizará ni revelará directa o indirectamente Información propiedad de PROTEOMIKA ni completa ni parcialmente excepto en lo pactado en este acuerdo.

3. **Excepciones**

3.1. Las anteriores restricciones impuestas a PROTEOMIKA no se aplicarán a Información propiedad del Trabajador que:

3.1.1 el trabajador pueda probar que se encontraba en su posesión y a su libre disposición antes de la revelación efectuada por parte de PROTEOMIKA

3.2.3 sea pública o pase a estar disponible al público, siempre que no sea mediante ni por culpa del trabajador.

3.2. Sin perjuicio de las restricciones establecidas a PROTEOMIKA y al Trabajador en el Artículo 2 del presente acuerdo, el Trabajador podrá revelar Información propiedad de PROTEOMIKA cuando tal revelación obedezca a un requerimiento o petición formal por parte de un Tribunal o cualquier otra autoridad gubernamental, siempre que previamente se le haya notificado tal petición a PROTEOMIKA y se le haya dado a la misma – si fuera posible- la oportunidad de oponerse a la necesidad de dicha revelación y/ o se le haya permitido solicitar una orden protectora o medida cautelar el objeto de que la Información revelada en virtud de esta petición, se utilice única y exclusivamente para el objeto para el que se dictó dicho requerimiento legal.

4. **Propiedad industrial**

Todos los derechos de propiedad intelectual y/o industrial que se pudieran contener en la Información revelada o desarrollada por Proteomika desde su constitución, como la Información revelada o desarrollada durante el periodo en el que el trabajador es contratado por la empresa, son propiedad de PROTEOMIKA, y que en consecuencia el trabajador no tendrá derecho de naturaleza alguno sobre dicha Información revelada o desarrollada.

5. **Daños y perjuicios**

El contravenir este acuerdo deparará cuantas consecuencias preceptúe el ordenamiento jurídico así como cuantos daños y perjuicios pudiere inferir a Proteomika.

6. **Duración del Acuerdo**

Las condiciones del presente acuerdo serán vigentes durante el periodo de vigencia del contrato de trabajo en la empresa, y en el caso de que el trabajador abandonara la Empresa, un periodo de diez (10) años a partir de la fecha de cese del contrato de trabajo.

7. **Ley aplicable**

La validez, interpretación y cumplimiento del presente acuerdo se regirá por las leyes y normativa española aplicables a la misma.

8. **Jurisdicción**

Ambas partes contratantes, con renuncia a cualquier fuero propio que pueda corresponderles, se someten a la jurisdicción de los jueces y Tribunales de Barcelona para cualquier acción que pudiera derivarse de la interpretación o cumplimiento del presente contrato.

Y, en prueba de conformidad con cuanto antecede, ratificándose en todas y cada una de sus manifestaciones y estipulaciones, firman por duplicado y a un solo efecto el presente documento, en lugar y fecha "ut supra".

Firma:_____
Nombre: Laureano Simón Buela
Cargo: Consejero Delegado
En nombre y representación de PROTEOMIKA, S.L.

Firma:_____
Nombre: Miguel Angel Molina Vila

PROGENIKA BIOPHARMA, S.A.
Edificio 801 . Parque Tecnológico de Zamudio
48160 Derio . Spain
Phone: +34 94 406 45 25
Fax: +34 94 406 45 26
www.progenika.com

PROGENIKA

To: JUAN ARIAS

From: LAUKEANO SIMON

Saludos

CONTRATO DE TRABAJO DE DURACION DETERMINADA

MINISTERIO DE TRABAJO
Y ASUNTOS SOCIALES
Instituto Nacional de Empleo

OFICINA DE EMPLEO
GETXO

Sello de registro del Servicio Público de Empleo: 2 7 MAY 2003

ESTA DILIGENCIA NO SUPONE PRONUNCIAMIENTO SOBRE EL CONTENIDO DEL DOCUMENTO

Código de contrato

- [X] Tiempo completo:
  - [X] Obra o Servicio Determinado — 401
  - [ ] Eventual por circunstancias de la producción — 402
  - [ ] Interinidad — 410
- [ ] Tiempo Parcial:
  - [ ] Obra o Servicio Determinado — 501
  - [ ] Eventual por circunstancias de la producción — 502
  - [ ] Interinidad — 510
- [ ] Situación jubilación parcial — 540

DATOS DE LA EMPRESA

CIF/NIF: B62793526

D/Dª: Antonio Martinéz Martinéz — NIF/NIE: 27460766P — En concepto (1): Apoderado

Nombre o Razón Social de la Empresa: PROTEOMIKA, S.L. — Domicilio Social: JOSEP SAMITIER, 1-5

País: — Municipio: 08028 — C. Postal: 08028

DATOS DE LA CUENTA DE COTIZACION

Régimen: 0111 — Cod.prov.: 08 — Número: 1370200 — Dig.contr.: 04 — Actividad Económica: Inv.Cient. y Tec. Co

DATOS DEL CENTRO DE TRABAJO

País: — Municipio:

DATOS DEL/DE LA TRABAJADOR/A

D/Dª: MIGUEL MOLINA VILA — NIF/NIE: 33895291F — Fecha de nacimiento: 02-03-65

Nº afiliación a la S.S.: 081008741563 — Nivel formativo: DOCTORADO — Nacionalidad:

Municipio del domicilio: — País domicilio:

Con la asistencia legal, en su caso, de D/Dª .....
N.I.F/NIE....., en calidad de (2) .....

DECLARAN

Que reúnen los requisitos exigidos para la celebración del presente contrato y, en consecuencia acuerdan formalizarlo con arreglo a las siguientes:

CLAUSULAS

Primera: La persona contratada prestará sus servicios como (3) .....Investigador..... incluido en el grupo profesional/categoría/nivel (4) .....Investigadora..... de acuerdo con el sistema de clasificación profesional vigente en la empresa.

Segunda: La jornada de trabajo será (5):

- [X] **A tiempo Completo:** la jornada de trabajo será de .....40..... horas semanales, prestadas de .....Lunes..... a .....Viernes.. con los descansos que establece la Ley.
- [ ] **A tiempo Parcial:** la jornada de trabajo ordinaria será de .....horas : Al día [ ] A la semana [ ] Al mes [ ] Al año [ ] . siendo esta jornada inferior a (6):
  - [ ] La de un trabajador a tiempo completo comparable.
  - [ ] La jornada a tiempo completo prevista en el Convenio Colectivo de aplicación.
  - [ ] La jornada máxima legal.

  La distribución del tiempo de trabajo será
  .....
  .....

(1) Directoría, Gerente, etc.
(2) Padre, madre, tutor/a o persona o institución que le/la tenga a su cargo.
(3) Indicar profesión.
(4) Señalar el grupo profesional y la categoría o nivel profesional que corresponda, según el sistema de clasificación profesional vigente en la empresa.
(5) Marque con una X lo que corresponda
(6) Marque con una X la situación que corresponda

PE/177

Tercera: La duración del presente contrato se extenderá desde 27-05-03 hasta 26-05-04
Se establece un periodo de prueba de (7) S/ Estatuto Trabajadores
En caso de que el convenio colectivo permita una duración mayor a la establecida legalmente, señálelo con una X: ☐

Cuarta: El/la trabajador/a percibirá una retribución total de 28550 euros brutos (8) Anuales
que se distribuye en los siguientes conceptos salariales (9) Salario Base y Plus COnvenio
En el supuesto del contrato para sustituir a trabajadores en formación por trabajadores beneficiarios de prestaciones por desempleo, el trabajador desempleado contratado percibirá la prestación contributiva o el subsidio por desempleo a que tenga derecho. El empresario durante el período de percepción de la prestación o subsidio que se compatibiliza, deberá abonar al trabajador la diferencia entre la cuantía de la prestación o subsidio por desempleo y el salario que le corresponde, siendo asimismo responsable de la totalidad de las cotizaciones a la Seguridad Social por todas las contingencias y por el total del salario indicado incluyendo el importe de la prestación o el subsidio.

Quinta : Las vacaciones anuales serán de (10) 30 días naturales (Prop. al tiempo trabajado)

Sexta : El contrato de duración determinada se celebra para:

☒ La realización de la obra o servicio (11) Identificación de mamarcadores en cancer de veiiga, teniendo dicha obra autonomía y sustantividad propia dentro de la actividad de la empresa.

☐ Atender las exigencias circunstanciales del mercado, acumulación de tareas o exceso de pedidos, consistentes en .....(12), aún tratándose de la actividad normal de la empresa. En caso de que se concierte por un plazo inferior a la duración máxima legal o convencionalmente establecida podrá prorrogarse, mediante acuerdo de las partes, por una única vez, sin que la duración total del contrato pueda exceder de dicha duración máxima.

☐ Sustituir al trabajador ..... (13), siendo la causa:

- ☐ Sustituir a trabajadores con derecho a reserva del puesto de trabajo
- ☐ Sustituir a trabajadoras por maternidad, sin bonificación de cuotas.
- ☐ Sustituir a trabajadores excedentes por cuidado de familiares, siendo el trabajador que sustituye al excedente, perceptor, durante más de un año, de prestaciones por desempleo de nivel contributivo o asistencial (Disposición Adicional 14ª del Real Decreto Legislativo 1/95).
- ☐ Para cubrir temporalmente un puesto de trabajo durante el proceso de selección o promoción, para su cobertura definitiva.
- ☐ Sustituir a trabajadores en formación por trabajadores beneficiarios de prestaciones por desempleo (14). Se acompaña certificado expedido por la Administración Pública o entidad encargada de gestionar la formación.

El trabajador contratado desempeñará el puesto de trabajo de ..... (15).

☐ Reducir la jornada de trabajo y el salario en un ..... (16), cuando el trabajador reúna las condiciones generales exigidas para tener derecho a la pensión contributiva de jubilación de la Seguridad Social, con excepción de la edad, que habrá de ser inferior, como máximo, cinco años a la exigida, o cuando, reuniendo las citadas condiciones generales, hayan cumplido ya dicha edad.

Séptima: A la finalización del contrato, excepto en los casos de contrato de interinidad, el trabajador tendrá derecho a recibir una indemnización de cuantía equivalente a la parte proporcional de la cantidad que resultaría de abonar ocho días de salario por cada año de servicio, o la establecida, en su caso, en la normativa específica que sea de aplicación.

Octava: El presente contrato se regulará por lo dispuesto en la legislación vigente que resulte de aplicación y particularmente por los artículos 12 y 15 del Estatuto de los Trabajadores, por la Ley 12/2001 de 9 de julio (B.O.E. de 10 de julio), y Real Decreto 2.720/1998, de 18 de diciembre (B.O.E. de 8 de enero) y en su caso, por lo establecido en la Disposición transitoria sexta del R.D.Ley 5/2002, de 24 de mayo (B.O.E. de 25 de mayo), por el que se desarrolla el citado art. 15 del Estatuto de los Trabajadores. Asimismo le será de aplicación lo dispuesto en el Convenio Colectivo de Quimicas

Novena: El contenido del presente contrato se comunicará al Servicio Público de Empleo de ....., en el plazo de los 10 días siguientes a su concertación.

Décima: Ambas partes se comprometen a comunicar el fin de la relación laboral a los Servicios Públicos de Empleo cuando ésta se produzca, de conformidad con lo establecido en el artículo 42.3 de la Ley 51/1980, de 8 de octubre, Básica de Empleo.

CLÁUSULAS ADICIONALES

" El trabajador renuncia a cualquier derecho sobre la propiedad intelectual derivado del trabajo a desarrollar en la Mercantil contratante"

Y para que conste, se extiende este contrato por triplicado ejemplar, en el lugar y fecha a continuación indicados, firmando las partes interesadas.
En Barcelona a 27 de Mayo de 20 03

El/la trabajador/a

El/la representante de la empresa

El/la representante legal del/de la menor, si procede
NO REPRESENTANTE SINDICAL

(7) Respetando lo establecido en el artículo 14.1 del Texto Refundidos de la Ley del Estatuto de los Trabajadores, aprobado por el Real Decreto Legislativo 1/1995, de 24 de marzo.
(8) Diarios, semanales o mensuales.
(9) Salario base y complementos salariales
(10) Mínimo: 30 días naturales.
(11) Identifique con claridad la obra o servicio, con autonomía y sustantividad propia dentro de la actividad de la empresa en la que prestara servicio el trabajador contratado
(12) Indíquese la causa o circunstancia que justifique la realización del contrato.
(13) Indíquese el nombre del trabajador sustituido.
(14) Solo para empresas de hasta 100 trabajadores y siempre que tales acciones formativas estén financiadas por cualquiera de las Administraciones Públicas (Art. 1do laDisposición transitoria sexta del R.D.Ley 5/2002.
(15) Indicar el el puesto de trabajo a desempeñar será el del/de la trabajador/a o del otro/a trabajador/a de la empresa que pase a desempeñar el puesto de aquel/aquella. Igualmente deberá identificarse, en su caso, el puesto de trabajo cuya cobertura definitiva se producirá tras el proceso de selección externa o promoción interna.
(16) Indicar el porcentaje de reducción de la jornada y del salario,éste será entre un 25 y un 85%.

ACUERDO MUTUO DE CONFIDENCIALIDAD

El presente **ACUERDO DE CONFIDENCIALIDAD** (en adelante "Acuerdo") se formaliza a 27 de mayo de 2002.

REUNIDOS

1. De una parte **Laureano Simón Buela**, con D.N.I. 35308166, Consejero Delegado de **PROTEOMIKA, S.L.** con domicilio a estos efectos en Joseph Samitier, 1-5, 08028 Barcelona, Barcelona, y C.I.F. B62793526 (en adelante "Proteomika ")

2. De otra parte, **Miguel Ángel Molina Vila** con D.N.I. 33895291F con domicilio en Barcelona (en adelante "el trabajador").

EXPONEN

1. Que PROTEOMIKA posee tanto información y tecnología confidencial relacionada con sus proyectos de I+D y los contratados por sus clientes como información relacionada con el negocio de PROTEOMIKA y sus empresas afiliadas incluyendo sin carácter limitativo, todos los datos comerciales y financieros así como también información relacionada de alguna forma.

2. Que el trabajador ha sido contratado por la Empresa como Investigador con fecha 27 de Mayo de 2002

3. Que para la realización normal del trabajo, PROTEOMIKA va a revelar Información al trabajador en los términos y condiciones que se especifican en este acuerdo.

ACUERDAN

1. **Interpretación**

El objetivo del presente acuerdo:

"Información de PROTEOMIKA": Incluye toda información propiedad de PROTEOMIKA sea cual sea su naturaleza, que dicha entidad considere que, por alguna u otra razón, no deba trascender a personas distintas de aquellas a quienes vaya estrictamente dirigida, incluyéndose en tal definición cualquier información, documentación y/o metodología desarrollada y/o elaborada por Proteomika desde su constitución así como la desarrollada y/o elaborada por las partes durante la vigencia del Contrato de Trabajo del Trabajador en la empresa.

2. **Compromisos**

PROTEOMIKA se compromete:

1. a revelar al trabajador toda la información necesaria para la normal realización de las tareas relacionadas con su puesto de trabajo en la empresa.

El Trabajador se compromete:

1. a utilizar toda la Información propiedad de PROTEOMIKA única y exclusivamente con el objeto de realizar las tareas necesarias para el normal desempeño de su trabajo en la empresa;

2. a mantener la confidencialidad de la Información propiedad de PROTEOMIKA a la que tenga acceso sea cual sea la forma por la que el mismo haya tenido conocimiento de dicha información; y

3. a devolver, todos los documentos y demás material en posesión custodia o control del trabajador, que contengan o incorporen parte de la Información propiedad de PROTEOMIKA, una vez que el trabajador deje de estar contratado por la empresa.

De conformidad con las obligaciones anteriores, el Trabajador no utilizará ni revelará directa o indirectamente Información propiedad de PROTEOMIKA ni completa ni parcialmente excepto en lo pactado en este acuerdo.

3. **Excepciones**

3.1. Las anteriores restricciones impuestas a PROTEOMIKA no se aplicarán a Información propiedad del Trabajador que:

3.1.1 el trabajador pueda probar que se encontraba en su posesión y a su libre disposición antes de la revelación efectuada por parte de PROTEOMIKA

3.2.3 sea pública o pase a estar disponible al público, siempre que no sea mediante ni por culpa del trabajador.

3.2. Sin perjuicio de las restricciones establecidas a PROTEOMIKA y al Trabajador en el Artículo 2 del presente acuerdo, el Trabajador podrá revelar Información propiedad de PROTEOMIKA cuando tal revelación obedezca a un requerimiento o petición formal por parte de un Tribunal o cualquier otra autoridad gubernamental, siempre que previamente se le haya notificado tal petición a PROTEOMIKA y se le haya dado a la misma – si fuera posible- la oportunidad de oponerse a la necesidad de dicha revelación y/ o se le haya permitido solicitar una orden protectora o medida cautelar el objeto de que la Información revelada en virtud de esta petición, se utilice única y exclusivamente para el objeto para el que se dictó dicho requerimiento legal.

4. **Propiedad industrial**

Todos los derechos de propiedad intelectual y/o industrial que se pudieran contener en la Información revelada o desarrollada por Proteomika desde su constitución, como la Información revelada o desarrollada durante el periodo en el que el trabajador es contratado por la empresa, son propiedad de PROTEOMIKA, y que en consecuencia el trabajador no tendrá derecho de naturaleza alguno sobre dicha Información revelada o desarrollada.

5. **Daños y perjuicios**

El contravenir este acuerdo deparará cuantas consecuencias preceptúe el ordenamiento jurídico así como cuantos daños y perjuicios pudiere inferir a Proteomika.

6. **Duración del Acuerdo**

Las condiciones del presente acuerdo serán vigentes durante el periodo de vigencia del contrato de trabajo en la empresa, y en el caso de que el trabajador abandonara la Empresa, un período de diez (10) años a partir de la fecha de cese del contrato de trabajo.

7. **Ley aplicable**

La validez, interpretación y cumplimiento del presente acuerdo se regirá por las leyes y normativa española aplicables a la misma.

8. **Jurisdicción**

Ambas partes contratantes, con renuncia a cualquier fuero propio que pueda corresponderles, se someten a la jurisdicción de los jueces y Tribunales de Barcelona para cualquier acción que pudiera derivarse de la interpretación o cumplimiento del presente contrato.

Y, en prueba de conformidad con cuanto antecede, ratificándose en todas y cada una de sus manifestaciones y estipulaciones, firman por duplicado y a un solo efecto el presente documento, en lugar y fecha "ut supra".

Firma:_____
Nombre: Laureano Simón Buela
Cargo: Consejero Delegado
En nombre y representación de PROTEOMIKA, S.L.

Firma:_____
Nombre: Miguel Angel Molina Vila

Juan Arias

De: Laureano Simon [lsimon@progenika.com]
Enviado: miércoles, 08 de febrero de 2006 21:21
Para: Beatriz Rodera [ABG PATENTES]
CC: Juan Arias
Asunto: Re: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimados amigos: Miguel Molina firmó en su día, como todos los empleados de Progenika y Proteomika, yo incluido, un documento de renuncia a favor de Proteomika sobre cualquie derecho de propiedad intelectual generada de su trabajo en la empresa. Y adicionalmente esta renuncia también figura como claúsula adicional en su contrato laboral enviado a la Seguridad Social
Os envío por fax ambos contratos.
Gracias
Laureano.

----- Original Message -----
From: Beatriz Rodera [ABG PATENTES]
To: 'Laureano Simon'
Cc: Juan Arias
Sent: Wednesday, February 08, 2006 11:00 AM
Subject: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Simón:

En relación a la solicitud de patente de la referencia, le adjuntamos el e-mail que nos ha escrito el Sr. Molina.

- Respecto a la primera pregunta que nos plantea, entendemos que no hay ningún problema en cambiar la dirección ya que no es trabajador de Progenika Biopharma, S.A.
- Respecto a la segunda cuestión, entendemos que debemos comunicarle que si firma el documento de "Assignment" perderá cualquier derecho sobre la invención y no recibirá ninguna compensación económica.

El hecho de comunicarle esta perdida de derechos dificultará la firma del documento por el inventor, por lo que podemos hacerle referencia a el Articulo 15.1 de la Ley de Patentes (11/1986) en el que se cita al empresario como propietario único de la invención y a el Artículo 18.2 de la Ley de Patentes (11/1986) en el se cita que el trabajador debe prestar su colaboración.

Articulo 15.1 de la Ley de Patentes (11/1986) "Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario"

Articulo 18.2 de la Ley de Patentes (11/1986) "Tanto el empresario como el trabajador deberán prestar su colaboración en la medida necesaria para la efectividad de los derechos reconocidos en el presente Título, absteniéndose de cualquier actuación que pueda redundar en detrimento de tales derechos"

En espera de sus instrucciones, le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Miguel Molina [mailto:miguelamol@hotmail.com]
Enviado el: miércoles, 08 de febrero de 2006 9:38
Para: brodera@abgpatentes.com
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Sra. Rodera:

He leído atentamente los documentos que me envío, y se me han planteado un par de dudas más que me gustaría resolver antes de firmarlos

-En la Patent Application se afirma que mi residencia es el Parque Tecnológico de Zamudio cuando, como usted ya sabrá, yo ya no trabajo para Progenika (antigua Proteomika)

-En el Assignment of Patent Application se dice que, por diez dólares, "the applicants... transfer unto said asignee (Progenika) the full and exclusive right to the said invention". Por tanto, interpreto que si la patente se llegase a vender o tuviese alguna vez una aplicación comercial, el beneficiario exclusivo sería Progenika, sin que yo recibiese compensación económica alguna.

Esperando su respuesta, atentamente

Miguel A Molina

From: *"Beatriz Rodera [ABG PATENTES]" <brodera@abgpatentes.com>*
To: *"'Miguel Molina'" <miguelamol@hotmail.com>*
CC: *"Juan Arias" <jarias@abgpatentes.com>*
Subject: *RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC*
Date: *Tue, 7 Feb 2006 16:09:41 +0100*

Estimado Sr. Molina:

Muchas gracias por su rápida respuesta.

Será suficiente que nos lo mande por correo, a poder ser certificado, ya que necesitamos los documentos en los que aparezcan las firmas originales tanto de Vd. como de un testigo.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: miércoles, 08 de febrero de 2006 11:01
Para: 'Laureano Simon'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: RV: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC
Importancia: Alta

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

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Articulo 15.1 de la Ley de Patentes (11/1986) "Las invenciones, realizadas por el trabajador durante la vigencia de su contrato o relación de trabajo o de servicios con la empresa, que sean fruto de una actividad de investigación explícita o implícitamente constitutiva del objeto de su contrato, pertenecen al empresario"

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-----Mensaje original-----
De: Miguel Molina [mailto:miguelamol@hotmail.com]
Enviado el: miércoles, 08 de febrero de 2006 9:38
Para: brodera@abgpatentes.com
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Sra. Rodera:

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-En el Assignment of Patent Application se dice que, por diez dólares, "the applicants... transfer unto said asignee (Progenika) the full and exclusive right to the said invention". Por tanto, interpreto que si la patente se llegase a vender o tuviese alguna vez una aplicación comercial, el beneficiario exclusivo sería Progenika, sin que yo recibiese compensación económica alguna.

Esperando su respuesta, atentamente

Miguel A Molina

From: *"Beatriz Rodera [ABG PATENTES]" <brodera@abgpatentes.com>*
To: *"'Miguel Molina'" <miguelamol@hotmail.com>*
CC: *"Juan Arias" <jarias@abgpatentes.com>*
Subject: *RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC*
Date: *Tue, 7 Feb 2006 16:09:41 +0100*

Estimado Sr. Molina:

Muchas gracias por su rápida respuesta.

Será suficiente que nos lo mande por correo, a poder ser certificado, ya que necesitamos los documentos en los que aparezcan las firmas originales tanto de Vd. como de un testigo.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

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Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

Beatriz Rodera [ABG PATENTES]

De: Miguel Molina [miguelamol@hotmail.com]
Enviado: miércoles, 08 de febrero de 2006 9:38
Para: brodera@abgpatentes.com
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

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Miguel A Molina

From: *"Beatriz Rodera [ABG PATENTES]" <brodera@abgpatentes.com>*
To: *"'Miguel Molina'" <miguelamol@hotmail.com>*
CC: *"Juan Arias" <jarias@abgpatentes.com>*
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Sin otro particular le saluda atentamente,

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Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: martes, 07 de febrero de 2006 16:10
Para: 'Miguel Molina'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimado Sr. Molina:

Muchas gracias por su rápida respuesta.

Será suficiente que nos lo mande por correo, a poder ser certificado, ya que necesitamos los documentos en los que aparezcan las firmas originales tanto de Vd. como de un testigo.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Miguel Molina [mailto:miguelamol@hotmail.com]
Enviado el: martes, 07 de febrero de 2006 15:07
Para: brodera@abgpatentes.com
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Sra. Rodera

Muchas gracias por enviar los documentos, los firmaré esta misma semana. Me queda sin embargo una duda: ¿qué procedimiento debo seguir para devolverlos? ¿correo ordinario, fax o adjunto a mensaje de correo electrónico (en formato pdf)?

Atentamente,

Miguel A Molina

From: *"Beatriz Rodera [ABG PATENTES]" <brodera@abgpatentes.com>*
To: *<miguelamol@hotmail.com>*
CC: *"Juan Arias" <jarias@abgpatentes.com>,"'Laureano Simon'" <lsimon@progenika.com>*
Subject: *Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC*
Date: *Tue, 7 Feb 2006 10:57:04 +0100*

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Molina:

En relación a la solicitud de patente de la referencia y según instrucciones de D. Juan Arias, le informamos que nos estamos ocupando de la tramitación de dicha solicitud en Estados Unidos. D. Gregorio Valencia nos ha proporcionado su dirección de e-mail para contactar con Vd. y así poder enviarle los documentos de **"Declaration and Power of Attorney"** y **"Assignment"** para que por favor proceda a fechar y firmar ambos documentos necesarios para la tramitación en dicho país y de esta manera poder presentarlos ante la Oficina de Patentes de Estados Unidos (USPTO), tal y como establece el Articulo 18.2 de la Ley de Patentes (11/1986).

Para el caso del documento de "Assignment" se necesita también la firma de un testigo con el fin de dar validez a este documento.

Muchas gracias por su colaboración.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1
Fax: +34 91 417 1
brodera@abgpatentes.c
http://www.abgpatentes.c

>>< Assignment-P1121USPC.doc >>

>>< DeclarationandPowerofAttorneyfinal-P1121USPC.doc >>

Beatriz Rodera [ABG PATENTES]

De: Miguel Molina [miguelamol@hotmail.com]
Enviado: martes, 07 de febrero de 2006 15:07
Para: brodera@abgpatentes.com
Asunto: RE: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Sra. Rodera

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Atentamente,

Miguel A Molina

From: *"Beatriz Rodera [ABG PATENTES]" <brodera@abgpatentes.com>*
To: *<miguelamol@hotmail.com>*
CC: *"Juan Arias" <jarias@abgpatentes.com>,"'Laureano Simon'" <lsimon@progenika.com>*
Subject: *Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC*
Date: *Tue, 7 Feb 2006 10:57:04 +0100*

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Molina:

En relación a la solicitud de patente de la referencia y según instrucciones de D. Juan Arias, le informamos que nos estamos ocupando de la tramitación de dicha solicitud en Estados Unidos. D. Gregorio Valencia nos ha proporcionado su dirección de e-mail para contactar con Vd. y así poder enviarle los documentos de **"Declaration and Power of Attorney"** y **"Assignment"** para que por favor proceda a fechar y firmar ambos documentos necesarios para la tramitación en dicho país y de esta manera poder presentarlos ante la Oficina de Patentes de Estados Unidos (USPTO), tal y como establece el Articulo 18.2 de la Ley de Patentes (11/1986).

Para el caso del documento de "Assignment" se necesita también la firma de un testigo con el fin de dar validez a este documento.

Muchas gracias por su colaboración.

Sin otro particular le saluda atentamente,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

>>< Assignment-P1121USPC.doc >>

>>< DeclarationandPowerofAttorneyfinal-P1121USPC.doc >>

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: martes, 07 de febrero de 2006 10:57
Para: 'miguelamol@hotmail.com'
CC: Juan Arias (jarias@abgpatentes.com); 'Laureano Simon'
Asunto: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

Assignment of Patent Application

Whereas, we, **Antonio Martínez Martínez, Laureano Simón Buela, Simón Santa Cruz, María Pilar Sáenz Jiménez, Miguel Molina Vila, Corina Junquera Sánchez-Vallejo, José Javier Gómez Román and Jorge Cuevas González**, hereafter referred to as applicants, have invented certain new and useful improvements relating to an **IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA**

[ ] for which an application for a United States patent was filed on _____, Application Number _____.

[ ] for which an application for a United States Patent was executed on _____, and

Whereas, **PROGENIKA BIOPHARMA, S.A.**, herein referred to as assignee, whose post office address is **Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª plantaE-48160 - DERIO – Vizcaya, Spain**, is desirous of acquiring the entire right, title and interest in the same:

Now, therefore, in consideration of the sum of ten dollars ($10.00), the receipt whereof is acknowledged, and other good and valuable consideration, we, the applicants, by these presents do sell, assign and transfer unto said assignee the full and exclusive right to the said invention in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof, and the entire right, title and interest in and to any and all Patents which may be granted therefor in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions, reissues, prolongations and extensions thereof. we hereby authorize and request the Commissioner of Patents and Trademarks to issue said United States Patent to said assignee, of the entire right, title, and interest in and to the same, for its sole use and behoof; and for the use and behoof of its legal representatives, to the full end of the term for which said Patent may be granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

The undersigned hereby grant the firm of Kramer and Amado, P.C. the power to insert on this document any identification which may be necessary or desired to reference the property being transferred under the rules of the United States Patent and Trademark Office for recordation purposes.

EXECUTED THIS __ day of _____, 20___, at _____

_____ _____

Antonio Martínez Martínez Date

_____

Witness

Assignment of Patent Application

Laureano Simón Buela _____ Date _____

Witness _____

Simón Santa Cruz _____ Date _____

Witness _____

María Pilar Sáenz Jiménez _____ Date _____

Witness _____

Corina Junquera Sánchez-Vallejo _____ Date _____

Witness _____

José Javier Gómez Román _____ Date _____

Witness _____

Jorge Cuevas González _____ Date _____

Witness _____

Assignment of Patent Application

_____ _____

Miguel Molina Vila Date

_____

Witness

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

As a below named inventor, I hereby declare that:
My residence/post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA
the specification of which is attached hereto unless the following box is checked:

(X) was filed on March 25, 2004 as PCT International Application Number PCT/EP04/003219 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose all information which is material to patentability as defined in 37 CFR 1.56.

Foreign Application(s) and/or Claim of Foreign Priority

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 of any foreign application(s) for patent or inventor(s) certificate listed below and have also identified below any foreign application for patent or inventor(s) certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE FILED	PRIORITY CLAIMED UNDER 35 U.S.C. 119
PCT	PCT/EP04/003219	03/25/2004	YES: NO: X
Spain	P200300708	03/26/2003	YES: X NO:

Provisional Application

I hereby claim the benefit under Title 35, United States Code Section 119(e) of any United States provisional application(s) listed below:

APPLICATION SERIAL NUMBER	FILING DATE

U.S. Priority Claim

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NUMBER	FILING DATE	STATUS (patented/pending/abandoned)

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Power of Attorney:
As a named inventor, I hereby appoint the attorney(s) and/or agent(s) under Customer Number 30868 to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Send correspondence to:	Direct telephone calls to:
Arlir M. Amado Kramer & Amado, P.C. 1725 Duke Street, Suite 240 Alexandria, VA 22314 Phone: (703) 519-9801 Fax: (703) 519-9802	Arlir M. Amado (703) 519-9801

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: Antonio Martínez Martínez Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

_____ _____
Inventor's Signature Date

Full Name of Inventor: Laureano Simón Buela Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

_____ _____
Inventor's Signature Date

Full Name of Inventor: Simón Santa Cruz Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

_____ _____
Inventor's Signature Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: María Pilar Sáenz Jiménez Citizenship: Spain

Residence: Edificio 801A. Parque Tecnológico de Zamudio, E-48160 Derio, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Corina Junquera Sánchez-Vallejo Citizenship: Spain

Residence: Parque Tecnológico de Zamudio, Ibaizabal Bidea - Edificio 801 - A 2ª planta, E-48160 DERIO – Vizcaya, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: José Javier Gómez Román Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/n E-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

Full Name of Inventor: Jorge Cuevas González Citizenship: Spain

Residence: HOSPITAL UNIVERSITARIO MARQUÉS DE VALDECILLA, Avda. Valdecilla s/n E-39008 Santander, Spain

Post Office Address: Same

Inventor's Signature Date

PATENT APPLICATION

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION
ATTORNEY DOCKET NO. ABG 3008 **CUSTOMER NUMBER:** 30868

Full Name of Inventor: Miguel Molina Vila Citizenship: Spain

Residence: Edificio 801A. Parque Tecnológico de Zamudio, E-48160 Derio, Spain

Post Office Address: Same

Inventor's Signature Date

Beatriz Rodera [ABG PATENTES]

De: Juan Arias [jarias@abgpatentes.com]
Enviado: martes, 07 de febrero de 2006 10:06
Para: 'Miguel Molina'; gvpqbp@iiqab.csic.es
CC: genqbp@yahoo.es; 'Beatriz Rodera [ABG PATENTES]'
Asunto: RE: Contacto con Miguel Angel Molina

Estimado Sr. Molina:

Gracias por su e-mail.

En breve recibirá un e-mail de Beatriz Rodera (ABG patentes) en el que le detallará el motivo por el cual nos hemos puesto en contacto con usted (firma de un documento).

Reciba un saludo cordial

Juan Arias Sanz
Partner
M.Sc. (Chemistry)
Spanish Patent Agent / European Patent Attorney

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
jarias@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Miguel Molina [mailto:miguelamol@hotmail.com]
Enviado el: martes, 07 de febrero de 2006 9:32
Para: gvpqbp@iiqab.csic.es; jarias@abgpatentes.com
CC: genqbp@yahoo.es
Asunto: RE: Contacto con Miguel Angel Molina

Estimado Sr. Arias

A través de los Drs. Gregorio Valencia y Gemma Espuña me ha llegado la noticia de que deseaba vd. contactar conmigo. Puede encontrarme en esta dirección de correo electrónico.

Atentamente,

Miguel A Molina

From: *Gregorio Valencia <gvpqbp@iiqab.csic.es>*
To: *jarias@abgpatentes.com*
CC: *miguelamol@hotmail.com, genqbp@yahoo.es*

Subject: *Contacto con Miguel Angel Molina*
Date: *Mon, 06 Feb 2006 18:42:48 +0100*
>Sr. Juan Arias
>ABG Patentes
>Madrid
>
>Querido Juan,
>
>Efectivamente, como puedes ver en el mensaje, Gemma Espuña sigue en
>contacto con Miguel Angel Molina. En el encabezamiento del correo de
>respuesta de Gemma puedes encontrar la dirección de Miguel.
>
>Un abrazo, Gregorio
>
>
>
>
>
>
>
> >X-Original-To: gvpqbp@iiqab.csic.es
> >Delivered-To: gvpqbp@iiqab.csic.es
> >DomainKey-Signature: a=rsa-sha1; q=dns; c=nofws; s=s1024; d=yahoo.es;
> > h=Message-ID:Received:Date:From:Subject:To:In-Reply-To:MIME-Version:Content
> > -Type:Content-Transfer-Encoding;
> > b=J2OcTZeG07qg0ZpbNMz6f0dKRQU4U+D5yn9kzTmysPuV85T29QPTWR3o4rUIEYXx0Li5YuJM/
> > QIBUIrHNR1ZY4iBK+gADJ/xROI/B88uwADEkzXB8g6LFFBmOcUxHZr6yV8oUSESXFCKrpFHiQNd
> > Bgc0H9IxewObt1u2Krwlsuw= ;
> >Date: Sat, 4 Feb 2006 17:17:36 +0100 (CET)
> >From: Espuna Gemma <genqbp@yahoo.es>
> >Subject: RE: Vells temps
> >To: Gregorio Valencia <gvpqbp@iiqab.csic.es>,
> > Miguel Molina <miguelamol@hotmail.com>
> >X-imss-version: 2.031
> >X-imss-result: Passed
> >X-imss-scores: Clean:99.90000 C:2 M:3 S:5 R:5
> >X-imss-settings: Baseline:1 C:1 M:1 S:1 R:1 (0.0000 0.0000)
> >
> >Hola Gregori, Acabo de veure el teu missatge, perquè hem estat uns dies
> >a Cinqueterre, canviant lleugerament d'aires i aprofitant per estirar les
> >cames. I tant que sé com localitzar en Miguel Ángel Molina, seguim en
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> >la vida...a veure quina sorpresa t'espera...esperem que sigui bona (encara
> >que vingui dels ex-col.legues d'allà dalt!). Molts petons a tots dos.
> > Gemma P.D. Per cert, sembla que dilluns començaré una nova feina...a
> >veure quant dura aquesta vegada...és el meu primer contracte indefinit, tot
> >i que no sé si vol dir gran cosa això... :-))
> >
> ><> escribió:
> >Dra. Gemma Espuña
> >
> >Estimade Gemma,
> >
> >
> >M'acaba de trucar Juan Arias que és un patent officer que ens va redactar
> >les patents del diflunisal i el clioquinol. També ha redactat patent per
> >Med-Plant-Genetics. Et sona no?. Doncs ell sabia que nosaltres hi haviem
> >tingut una persona allí i per tant em demana si coneixem com es podria
> >localitzar a Miguel Angel Molina Vila. Esta a les teves mans?.
> >
> >Petons, Gregori
> >
> >NB. Ara mateix marxem a Zaragoza a un dels EPIs o sigui que fins dilluns no
> >et podré contestar
> >
> >
> >
> >

Beatriz Rodera [ABG PATENTES]

De: Juan Arias [jarias@abgpatentes.com]
Enviado: martes, 07 de febrero de 2006 9:48
Para: 'Beatriz Rodera [ABG PATENTES]'
Asunto: RV: Contacto con Miguel Angel Molina

FYI

Juan Arias Sanz
Partner
M.Sc. (Chemistry)
Spanish Patent Agent / European Patent Attorney

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
jarias@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Miguel Molina [mailto:miguelamol@hotmail.com]
Enviado el: martes, 07 de febrero de 2006 9:32
Para: gvpqbp@iiqab.csic.es; jarias@abgpatentes.com
CC: genqbp@yahoo.es
Asunto: RE: Contacto con Miguel Angel Molina

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To: *jarias@abgpatentes.com*
CC: *miguelamol@hotmail.com, genqbp@yahoo.es*
Subject: *Contacto con Miguel Angel Molina*
Date: *Mon, 06 Feb 2006 18:42:48 +0100*
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>Madrid
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Juan Arias

De: Gregorio Valencia [gvpqbp@iiqab.csic.es]
Enviado: lunes, 06 de febrero de 2006 18:43
Para: jarias@abgpatentes.com
CC: miguelamol@hotmail.com; genqbp@yahoo.es
Asunto: Contacto con Miguel Angel Molina

Sr. Juan Arias
ABG Patentes
Madrid

Querido Juan,

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Un abrazo, Gregorio

>X-Original-To: gvpqbp@iiqab.csic.es
>Delivered-To: gvpqbp@iiqab.csic.es
>DomainKey-Signature: a=rsa-sha1; q=dns; c=nofws; s=s1024; d=yahoo.es;
> h=Message-ID:Received:Date:From:Subject:To:In-Reply-To:MIME-Version:Content
> -Type:Content-Transfer-Encoding;
> b=J2OcTZeG07qg0ZpbNMz6f0dKRQU4U+D5yn9kzTmysPuV85T29QPTWR3o4rUIEYXx0Li5YuJM/
> QIBUIrHNR1ZY4iBK+gADJ/xROI/B88uwADEkzXB8g6LFFBmOcUxHZr6yV8oUSESXFCKrpFHiQNd
> Bgc0H9IxewObt1u2Krwlsuw= ;
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>X-imss-version: 2.031
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>Petons, Gregori
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>NB. Ara mateix marxem a Zaragoza a un dels EPIs o sigui que fins
>dilluns no et podré contestar
>
>
>
>

Beatriz Rodera [ABG PATENTES]

De: Laureano Simon [lsimon@progenika.com]
Enviado: miércoles, 01 de febrero de 2006 14:01
Para: Beatriz Rodera [ABG PATENTES]
CC: Juan Arias; psaenz@proteomika.com
Asunto: Re: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

Estimada Beatriz:
Siguiendo vuestras instrucciones, hemos enviado la documentación a firmar a Miguel Angel Molina Vila, por correo certificado, 2 veces separadas por 15 dias; las cartas nos han sido devueltas y os hemos enviado a vosotros los sobres devueltos (sin abrir).
La dirección es la última que figura en la base de datos de la empresa.
No le hemos localizado haciendo búsquedas en internet.
Tras consulta al 11818, No hay ningún abonado telefónico en Barcelona (ciudad en la que residia), ni en la provincia con su nombre.
Saludos.
Laureano.

Laureano Simon.
Progenika biopharma, S.A.
Parque tecnológico de Zamudio. 801.
48160, Derio (Bilbao). Vizcaya. Spain.
Tel: +34 94 4064525
Fax: +34 94 4064526
www.progenika.com

----- Original Message -----
From: Beatriz Rodera [ABG PATENTES]
To: 'Laureano Simon'
Cc: Juan Arias
Sent: Wednesday, February 01, 2006 11:28 AM
Subject: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Simón:

En relación con la solicitud de patente de la referencia, le informamos que debido a la negativa de D. Miguel Ángel Molina Vila a firmar los documentos de "*Power of Attorney*" y de "*Assignment*", nuestros corresponsales en USA necesitan determinada información para preparar la documentación necesaria para presentar un escrito ante la Oficina Norteamericana de Patentes (USPTO).

Necesitaríamos, por tanto, que nos confirmen la siguiente información y que, en su caso, aporten la

documentación correspondiente:

1. Entendemos que no ha habido respuesta del inventor y que, por tanto, no ha habido ninguna negativa verbal o escrita a firmar los documentos. Por favor, confírmenos este punto.
2. Es importante tener la certeza de que la documentación ha sido enviada al "*last known address*" del inventor. Por tanto, sería necesario que nos confirme que así ha sido, y que aporte documentación que demuestre que Progénika ha confirmado la "*last known address*" que existe en el departamento de recursos humanos mediante consulta de las guías telefónicas (internet) o cualquier otro método. (Copias de la búsqueda en internet o de la guía telefónica serían convenientes)

Quedamos a la espera de sus comentarios.

Un saludo,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

****
*** REPORTE DE TX ***
****

TRANSMISIÓN OK

N° TRABAJO	3244
DIRECCIÓN DESTINO	0944064526
CLAVE/SUBDIR	
ID CONEXIÓN	PROGENIKA BIOPHARMA
HORA COM.	01/02 12:52
TP USADO	00'21
PÁGS.	2
RESULTADO	OK

abg
patentes
ARIAS , BERNARDO & GONZÁLEZ
Asesoría y Agencia de la Propiedad Industrial
Intellectual Property

PROGENIKA BIOPHARMA, S.A.
Parque Tecnológico de Zamudio
Ibaizabal Bidea - Edificio 801 - A
2ª planta
E-48160 - DERIO - Vizcaya

Atn.: D. Laureano Simon

Vía Fax
Confirmación por correo

N/Ref.:**P1121USPC**
S/Ref.:

Madrid, 1 de febrero de 2006

Asunto.: Solicitud de patente en Estados Unidos nº 10/550,608 por "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Estimado Sr. Simón:

En relación con la solicitud de patente de la referencia, le informamos que debido a la negativa de D. Miguel Ángel Molina Vila a firmar los documentos de "*Power of Attorney*" y de "*Assignment*", nuestros corresponsales en USA necesitan determinada información para preparar la documentación necesaria para presentar un escrito ante la Oficina Norteamericana de Patentes (USPTO).

Necesitaríamos, por tanto, que nos confirmen la siguiente información y que, en su caso, aporten la documentación correspondiente:

1. Entendemos que no ha habido respuesta del inventor...

patentes
ARIAS , BERNARDO & GONZÁLEZ
Asesoría y Agencia de la Propiedad Industrial
Intellectual Property

PROGENIKA BIOPHARMA, S.A.
Parque Tecnológico de Zamudio
Ibaizabal Bidea - Edificio 801 - A
2ª planta
E-48160 - DERIO - Vizcaya

Atn.: D. Laureano Simon

Vía Fax
Confirmación por correo

N/Ref.:**P1121USPC**
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Madrid, 1 de febrero de 2006

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1. Entendemos que no ha habido respuesta del inventor y que, por tanto, no ha habido ninguna negativa verbal o escrita a firmar los documentos. Por favor, confirmenos este punto.
2. Es importante tener la certeza de que la documentación ha sido enviada al "*last known address*" del inventor. Por tanto, sería necesario que nos confirme que así ha sido, y que aporte documentación que demuestre que Progénika ha confirmado la "*last known address*" que existe en el departamento de recursos humanos mediante consulta de las guías telefónicas (internet) o cualquier otro método. (Copias de la búsqueda en internet o de la guía telefónica serían convenientes)

Quedamos a la espera de sus comentarios.

Un saludo,

Juan Arias Sanz
European Patent Attorney
ABG Patentes, S.L.

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: miércoles, 01 de febrero de 2006 11:29
Para: 'Laureano Simon'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: Solicitud de patente en Estados Unidos No. 10/550,608- N/Ref.: P1121USPC
Importancia: Alta

N/Ref.: P1121USPC

Asunto: Solicitud de patente en Estados Unidos No. 10/550,608 con título "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

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Quedamos a la espera de sus comentarios.

Un saludo,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

Beatriz Rodera [ABG PATENTES]

De: Arlir Amado [arlir@kramerip.com]
Enviado: martes, 31 de enero de 2006 17:16
Para: Beatriz Rodera [ABG PATENTES]
Asunto: RE: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008

Dear Beatriz:

I apologize for my delay. I've responded to your email directly below your questions. Let me know if these steps have been taken so we can move forward and prepare a statement of facts. If you can get back to me with a draft a statement, we'll then modify and return to you for review.

Regards,
Arly

O/Ref.: P1121USPC
Y/Ref.: AGB 3008

Re.: Patent Application in United States No.10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMA, S.A.

Dear Sirs:

This is in connection with your e-mail dated October 17, 2005, regarding the Declaration and Power of Attorney Form.

The Applicant has had problems in obtaining the signature of all of the inventors. Actually, the Applicant and one of the inventors had serious discussion and, as a consequence, the inventor no longer works for the Applicant and, further, he does not want to sign the Declaration and Power of Attorney Form.

The Applicant has sent us all the documentation regarding the several times he has sent the Form to the inventor.

We believe that you might need a report from the applicant answering the following questions to prepare and affidavit to be filed before the USPTO:

negativa
What were the circumstances of the refusal? When there is an express oral refusal, that fact along with the time and place of the refusal must be stated in the statement of facts. When there is an

express written refusal, a copy of the document evidencing that refusal must be made part of the statement of facts. The document may be redacted to remove material not related to the inventor's

reasons for refusal. Statements by a party not present when an oral refusal is made will not be accepted. MPEP 409.03(d).

(1) How do we know the address of the non-signing inventor and what steps were taken to verify that the address to which the declaration was sent is actually the correct address? What documentation is available to prove this? (e.g., printouts of recent internet searches, telephone directories, updated human resource records). I would try to obtain confirmation of the inventor's address and telephone number using a resource such as Ultimate White Pages; the MPEP only specifies that it is necesssary to send the papers to the "last known address," so if

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(2) What steps were taken by you to contact the non-signing inventor? (Here, you would describe how you mailed the declarations to the non-signing inventor's address three times, and the corresponding results of these mailing.) Also, it would be extremely useful if you searched for the telephone number of the non-signing inventor and tried to call him.

(3) For each action taken, what documentation can be provided to show that the step was actually done? In the case of the mailings, we already have the certified mail return receipts and the cover letters that you provided. As mentioned above, other helpful evidence would be printouts of internet searches to determine the telephone and/or address of the non-signing inventors.

Could you please confirm me you need this information and, if necessary, which further information and documents are needed?

Very truly yours

Beatriz Rodera Tobal
Formalities Department

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28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: martes, 17 de enero de 2006 13:52
Para: 'aamado@kramerip.com'
Asunto: US National Stage of PCT/EP2004/003219 - O/Ref.: P1121USPC - Y/Ref.: AGB 3008
Importancia: Alta

O/Ref.: P1121USPC
Y/Ref.: AGB 3008

Re.: Patent Application in United States No.10/550,608 with title "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" in the name of PROGENIKA BIOPHARMA, S.A.

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Could you please confirm me you need this information and, if necessary, which further information and documents are needed?

Very truly yours

Beatriz Rodera [ABG PATENTES]

De: Beatriz Rodera [ABG PATENTES] [brodera@abgpatentes.com]
Enviado: lunes, 26 de septiembre de 2005 15:20
Para: 'Laureano Simon'
CC: Juan Arias (jarias@abgpatentes.com)
Asunto: RE: Entrada en fase nacional en Estados Unidos - N/ Ref.: P1121USPC

Estimado Laureano:

No se les puede eliminar de la patente por las particularidades de la ley americana. Lo mejor que se puede hacer es enviar estos documentos ("Declaration and Power of Attorney" y "Assignment") a Miguel Molina Vila y a Jorge Cuevas González por correo certificado (al menos dos veces), para de esta forma tener un justificante de que se ha intentado conseguir su firma. Si aun así estas dos personas no lo firmaran, se presentarían estos documentos ante la Oficina de Patentes Norteamericana (USPTO) sin las firmas de estos dos inventores, pero así podremos justificar ante la USPTO que se ha hecho todo lo posible por conseguir su firma

No dude en contactar con nosotros para cualquier aclaración.

Un saludo,

Beatriz Rodera Tobal
Formalities Department

ABG PATENTES
Orense 68, 7ª Planta
28020 Madrid
(SPAIN)

Tel.: +34 91 417 1300
Fax: +34 91 417 1301
brodera@abgpatentes.com
http://www.abgpatentes.com

-----Mensaje original-----
De: Laureano Simon [mailto:lsimon@progenika.com]
Enviado el: lunes, 26 de septiembre de 2005 12:56
Para: Beatriz Rodera [ABG PATENTES]
CC: Cecilia Ranilla
Asunto: Re: Entrada en fase nacional en Estados Unidos - N/ Ref.: P1121USPC

Estimada Beatriz: Con dos de los autores, Miguel en Progenika y Jorge en Santander, no hay contacto en la actualidad. Se les puede eliminar de la patente?
Atentamente.
Laureano Simon.
Progenika biopharma, SA.

----- Original Message -----
From: Beatriz Rodera [ABG PATENTES]
To: lsimon@progenika.com
Cc: Cecilia Ranilla
Sent: Monday, September 26, 2005 12:42 PM
Subject: Entrada en fase nacional en Estados Unidos - N/ Ref.: P1121USPC

N/ Ref.: P1121USPC

Asunto: Entrada en fase nacional en Estados Unidos de la solicitud de patente internacional No. PCT/EP2004/003219 por "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Muy Sr. nuestro:

Beatriz Rodera [ABG PATENTES]

De: Laureano Simon [lsimon@progenika.com]
Enviado: lunes, 26 de septiembre de 2005 15:12
Para: Beatriz Rodera [ABG PATENTES]
CC: Cecilia Ranilla
Asunto: Re: Entrada en fase nacional en Estados Unidos - N/ Ref.: P1121USPC

Estimada Beatriz: Con dos de los autores, Miguel en Progenika y Jorge en Santander, no hay contacto en la actualidad; Miguel firmo en su dia un contrato, como todos los trabajadores de Progenika, renunciando a cualquier derecho de IP. Se les puede eliminar de la patente?
Gracias

Atentamente.
Laureano Simon.
Progenika biopharma, SA.

----- Original Message -----
From: Beatriz Rodera [ABG PATENTES]
To: lsimon@progenika.com
Cc: Cecilia Ranilla
Sent: Monday, September 26, 2005 12:42 PM
Subject: Entrada en fase nacional en Estados Unidos - N/ Ref.: P1121USPC

N/ Ref.: P1121USPC

Asunto: Entrada en fase nacional en Estados Unidos de la solicitud de patente internacional No. PCT/EP2004/003219 por "IN VITRO METHOD TO DETECT BLADDER TRANSITIONAL CELL CARCINOMA" a nombre de PROGENIKA BIOPHARMA, S.A.

Muy Sr. nuestro:

En relación a la solicitud de patente identificada en el asunto, adjunto remitimos los documentos de **"Declaration and Power of Attorney"** y **"Assignment"** para que sean debidamente firmados y fechados.
Para el caso del documento de "**Assignment**" también deberá ser firmado por un testigo con el fin de darle validez.

Por favor rogamos que cuando estén listos ambos documentos, nos lo remita a la mayor brevedad posible.

Sin otro particular se despide atentamente,

Beatriz Rodera Tobal
Formalities Department

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